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at Colorado Springs, Colorado
April 19, 20 and 21, 1950

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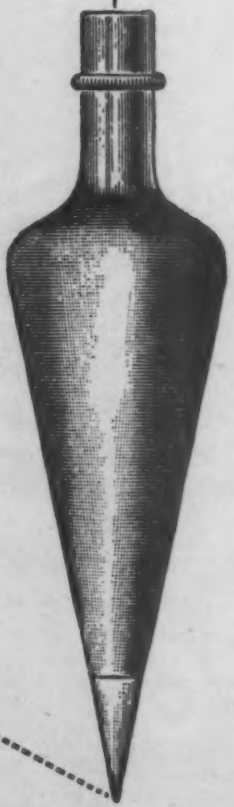

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TRANSACTIONS

OF THE

AMERICAN SURGICAL ASSOCIATION

MEETING HELD AT COLORADO SPRINGS, COLORADO, APRIL 19, 20, 21, 1950

ADDRESS OF THE PRESIDENT

THE TRAINING OF SURGEONS FOR SMALL COMMUNITIES

THOMAS G. ORR, M.D.

KANSAS CITY, KANSAS

IT IS NOW MY PLEASURE to express my sincere appreciation of the honor of serving as your President. Association with you has ever been to me a great inspiration, and with the passing of each of the 21 years of my membership in the American Surgical Association, I have grown more and more conscious of the privilege which is mine.

In my discussion today of the training of surgeons for small communities, I shall emphasize but one phase of surgical training, a subject that, through the years, has had an important place on many of our programs.

I am aware that I am speaking to a group of men who know what the qualifications of surgeons should be. It is, therefore, not my intention to present a new plan of surgical training, but rather, to urge a sympathetic understanding of the surgical needs of our small communities and offer a few suggestions which may increase your interest in the improvement of surgery in those towns and villages where major operative procedures are now being done by men with inadequate preparation.

To say that surgery is poorly done in all small communities would be a gross untruth. Let us read the opinion of Arthur Dean Bevan, made 21 years ago before this Association. He said, "I am surprised at the splendid work that is being done in the small hospitals everywhere in the United States. Go to California, or Texas, or Minnesota, or New England, and inspect these hospitals. You will find the very best work being done every-

where, work that is needed. The small hospitals of the country are caring for emergency cases that could not be sent to the great city hospitals. Recognizing the improvements that are still ahead of us, we should feel more enthusiastic about the splendid progress that is being made and the splendid work that is being done." No one will disagree with the above statement that there are many small hospitals throughout this country where first-class work is being done. We all agree that the efforts made by the American College of Surgeons, the American Medical Association, and the various Specialty Boards have greatly improved the quality of surgery in the last 21 years.

We know that there are many self-trained surgeons who are doing excellent work. As to what may have happened to some of their patients along the pathway to excellence, we can but speculate. Some of these surgeons may have had the misfortune, as Hippocrates has warned, to "exhibit the man maimed." I venture to express the opinion that each and every self-trained surgeon has a wish in his heart that he could have had adequate training before he began his life's work. It is true that our forefathers learned surgery by the "trial and error" method, but in modern times this method is not acceptable. Self-training in surgery is as obsolete as the old proprietary medical school training.

Why should we be interested in the small community surgeon? Because surgery is being done, will continue to be done, and should be done in small community hospitals. There is no logical reason why patients should be required to go to large medical centers for their surgery. There are many reasons why they should be able to have their surgery done near their homes. Not the least of these reasons is economy. In these days of mounting costs of medical care in general, many patients find the financial burden of surgery prohibitive when they must travel long distances to strange centers to have it done. The surgeon's fee is not the prohibitive factor in most instances. Hospitalization, travel, and the living expenses of relatives who accompany the patient, are the principal causes of increasing surgical costs. There are other reasons why patients may wish to remain near their homes for treatment. They prefer to be near their friends and relatives. Friendship for their local physician encourages patients to accept him as their surgeon. If a hospital exists in a community, local pride influences some people to patronize their home institution, and pressure even may be brought to bear upon patients to remain at home for treatment. These influences are likely to be potent if the community has financially assisted in the erecting and equipping of the hospital. It is clearly evident, in the trend of the times, that more surgery will be done in small communities.

The better a physician or surgeon is trained the more he will appreciate that all patients should not be treated in community hospitals. As far as we can see into the misty reaches of the future, there always will be certain types of surgery that should be sent to centers where men are especially trained for more difficult diagnoses and complex operations. And it should forever be the patient's privilege, in our democracy, to go where he wishes and travel

as far as he desires for his medical or surgical treatment, even if adequate facilities are available near his home.

Competency of the surgeon is an ever-present problem. There is no known way to compel a surgeon to practice within his limitations. His conscience is his only guide, and the elasticity of a man's conscience sometimes betrays him. Financial rewards are usually the greatest strain upon the doctor's conscience. Moral values are sometimes surrendered to money values. The blessed balm of anesthesia has given the untrained or the unscrupulous surgeon his opportunity for transgression. He may operate for complaints and not pathology. Our laws now permit a doctor of medicine to operate upon patients whether he knows a "hawk from a handsaw" or a colon from an ileum. In 1921, John B. Roberts, in his presidential address before this Association, disposed of the subject, "The Making of a Surgeon" in two printed pages. In his short discourse he recommended that "the mental and moral equipment of a medical graduate seeking professional and public support in his operative surgical efforts should be subjected to a searching analysis." The method of making this "searching analysis" is still a goal we have not reached. Although the prospect of improving surgery may, at times, be discouraging, our attitude toward the unqualified surgeon must be realistic. We cannot stem the tide of operators by speeches and incriminations. We, as surgeons, certainly possess the degree of judgment to believe as did Caesar that "It becomes all men, who deliberate on dubious matters, not to be influenced by hatred, affection, anger, or pity." If our doctors and their patients want community surgery, our efforts should always be helpful.

In recent years there has been a remarkable awakening of public interest in rural health. Much has been said about the need of general practitioners in small communities. Little has been said about the need of surgeons in such communities. Weir Mitchell recognized that "the rate of advance in medicine is to be tested by what the country doctor is." The same may be said of the country surgeon. Perhaps our thinking has been too much concerned with the training of surgeons for academic careers in the larger medical centers where research is emphasized. We cannot expect all of our trainees in surgery—no, not even a tenth part of them—to do research of any type. That small percentage of men who possess the spark to develop new fields in surgery must be the guiding lights for those who practice only the application of the art. For a better distribution of surgical talent it would be advisable that our choice residency services reserve places for men whose avowed intentions are to practice in our smaller cities. Since there is an uncontrollable as well as a desirable trend that surgery be done in community hospitals, it is our problem to furnish more trained surgeons and not more general practitioners who practice surgery. The welfare of patients would be better safeguarded if trained surgeons were general practitioners than if general practitioners were surgeons. I concur in the belief expressed by Sir William Ogilvie that "we should ensure that in every town and village where surgery is practiced there is a man well versed in the art and craft, if not necessarily in its science."

What is this "general practice" which is so much discussed today? It is difficult to define this type of practice. Certainly, if it means what the term implies, it includes surgery. But no single mind can encompass the entire field of medicine. General practice, as we once thought of it, is gradually disappearing. To give a patient the full benefit of present day medical care, practice must be more and more co-operative. Small communities would be better served by group practice. In general, patients believe that "going through a clinic" means better treatment and there is a growing tendency for them to go where group practice is available. Every medical school and organized clinic practices medicine by the group plan. Relatively small communities could support group practice clinics on a lesser scale. There are today many such clinics in existence where first class medical and surgical practice is being done. The influence of good working groups in well equipped general hospitals properly distributed would soon make the small, poorly equipped hospitals unprofitable.

It is recognized that improvement in surgical practice must be by evolution and not by revolution. To be able to place trained surgeons in small communities, there must be some incentive which does not exist at present. It is too much to hope that a young surgeon, who has worked his way through a satisfactory residency with all modern conveniences, will locate where up-to-date facilities and trained assistants do not exist. Means of attracting well-trained young surgeons to smaller community centers is, therefore, an urgent necessity.

Would additional new hospitals in small community centers improve surgery? Certainly increased hospital facilities would offer greater opportunities for well-trained young surgeons. New hospitals would also increase the opportunities of untrained operators, and perhaps lower the standards of surgery in some localities until the evolutionary process of making and placing qualified surgeons has had time to develop. A hospital is not a magic wand that will convert bad into good surgery, the apparent belief of some people to the contrary, notwithstanding. And it is certain that the public cannot always be depended upon to make an intelligent choice of surgeons.

Although the need for more hospitals seems definite, there is no need for small hospitals in every village and hamlet. There are now too many small hospitals. A survey made in my own state by the State Board of Health shows that 50 per cent of its hospitals have 25 beds or less. Of these small hospitals 27 per cent are converted residences, 33 per cent are potential fire hazards, and 22 per cent are more than 40 years old. The same survey estimates that 3000 more hospital beds are needed in the state. Reasoning from the standpoint of greatest efficiency it is doubtful if any general hospital of less than 50 beds should be built anywhere. This statement is not meant to imply that diagnostic centers should not be constructed; but it is inconceivable, in this modern age, that a hospital service can be efficient without a well-trained anesthetist, pathologist, and roentgenologist. The very small hos-

pitals cannot afford such service. A small hospital is often a financial liability for the owner and deficits are covered by the surgeon's fees. Surgery in a poorly equipped hospital is only a step in advance of the "horse and buggy" surgery formerly done in the home, and has no place in the modern care of surgical patients. General hospitals, with a minimum of 50 beds, could be located so that they would serve the needs of all small communities. The construction of such hospitals would probably meet with the approval of most of those physicians who now own their small hospitals. It is not a surgeon's obligation to provide a hospital in which he may treat his patients. The building of community hospitals is as much a public responsibility as is the building of schools and courthouses.

How can more and better surgeons be trained? Every surgeon should consider himself a teacher, and should devote some of his time to the training of young men. Such time is not lost, since there is nothing that adds to a man's intellectual stature like sincere teaching. Every possible facility in our country should be used as a training center. When we train young men in surgery we are not acting as our professional brothers' keepers, but as public benefactors. The proper training of surgeons is a serious task. The beginner in operative surgery should have close supervision. To permit him too much freedom results in bad habits and courts disaster for his patients. Those of you in this Association know that to teach surgery means standing on one side of an operating table assisting a novice on the other side, consuming your time and energy, when you could do the operation yourself in less time, with much less effort, and with less trial of patience. Any qualified surgeon is always conscious of the many pitfalls in surgical technic. He knows that the beginner in surgery cannot be taught by looking over a surgeon's shoulder, by seeing a motion picture, or by watching a television screen. This type of instruction is for the man who knows some surgery and is improving his learning. A beginner must be trained, as Grey Turner recently expressed it, "on living, quivering, pulsating human tissue." He can learn living pathology at the operating table and there only.

I am doubtful if our present training of surgeons for community practice is adequate in many of our surgical centers. In answer to a questionnaire recently sent to my own past residents, many of whom are located in small communities, all emphasized the importance of some training in the surgical specialties. Some of them stated that a large percentage of their practice is gynecology. The training of these men should be different from the training of men for academic careers. The community surgeon must be a general surgeon. He must be prepared to cope with emergencies in special surgical fields so that he may not make a bad situation worse before a specialist is available. Although it may be desirable, training in the surgical specialties is not indispensable to the surgeon who is to spend his life in a teaching institution where he works with specialists to whom he can always turn for help and advice.

Postgraduate education has acquired new momentum since World War II.

It appears probable that more funds will be available in the future for the training of graduates who have been in private practice. As a part of this training it would be desirable to have postgraduate surgical services in teaching hospitals, where a period of six months to two years in residency would be available to selected men in practice who wish to become better surgeons.

Two-year internships are now being offered to improve training for what is called general practice. Could not an additional year be considered, making a three-year training period to be spent in medicine, pathology, the surgical specialties, and general surgery? Would such a training be acceptable for the practice of surgery in a small community? I think it would be acceptable under present circumstances. Some may say that such a plan would sanction the lowering of surgical standards as sponsored by our standardizing agencies. This is very true, but what a great advance such training would be over that received by the "trial and error" surgeon with only an internship, who is now free to loose his untried talents on his unsuspecting patients. This plan would, at least, be a stepping-stone to better surgery until facilities are available for adequate training of every young surgeon. To encourage progress, selected men from this group, after a few years of satisfactory surgical practice, should be accepted for examination by the American Board of Surgery.

The future training of surgeons offers a financial problem of some magnitude. There are many brilliant young men who are without sufficient funds to continue graduate work in surgery after their intern year. Institutions offering graduate training should provide adequate salaries so that men may be selected as residents without considering their financial status. When the G. I. program has been terminated there will be increased demands upon institutions offering advanced training. These institutions should begin now to make plans for an increased budget for graduate education. If the public is to have an increasingly higher grade of medical care it should be educated to realize that graduate training is an integral part of medical education.

And now, finally, a speculative thought! What would happen to the education and placement of surgeons if socialized medicine were to become rampant in this nation? We cannot predict what restrictions might be placed upon the teaching and practice of surgery under a political bureaucracy. Robert Millikan, the physicist, in a recent discussion of "The Most Vital Problem in Education Today" made the significant remark that "local cancer in humans or in states can be eliminated before it has spread throughout the whole body, but when the whole system has become infected the patient dies, whether that patient be a man or a great federal republic." This statement is a dire prediction of what might happen under government control of education. We sincerely hope that any type of state or federal interference with medical education and the practice of medicine will never become an American reality. We look forward with enthusiasm to the day when our present methods of training physicians and surgeons will reach such a stage of efficiency that any thought of legislation to control medical practice further will be banished forever.

CONGESTIVE ATELECTASIS — A COMPLICATION OF THE INTRAVENOUS INFUSION OF FLUIDS*

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Paul Bert[4] described congestive atelectasis as a phenomenon attending rapid decompression. Hurtado[14] first described the microscopic appearance thereof in the lungs of guinea pigs. Fegler and Banister have performed well-controlled experimental studies upon its etiology relative to decompression. Their description of the gross and microscopic appearance of the lungs is as follows:

"Congestive atelectasis is the term chosen to describe a further lung change in which the microscopical picture showed maximal dilatation of the lung capillaries and complete exclusion of air from the alveolar spaces. Macroscopically the condition suggested gross hemorrhage. The areas affected were sharply limited and stood out from the surrounding tissue because of their liver-like, uniform, dark red coloration; thus they were readily distinguishable even when they co-existed with severe hyperemia in the same part of the lung. Closing the trachea before opening the chest intensified the contrast between hyperemia and congestive atelectasis. Inflation of the lung caused the congestive airless parts of the lung to disappear and a restoration of the normal pink coloration, which showed the condition to be congestive and not hemorrhagic. The areas affected by congestive atelectasis were not confined to a particular part of the lung surface nor to any one lobe. However, they seemed to develop more frequently around the hilum or on the dorsal surfaces."[10]

During the past nine years the gross and microscopic characteristics of congestive atelectasis in patients have been seen in more than 20 instances; and rapid decompression was not an etiologic factor in any case. The following case summaries present the clinical experience with the phenomenon during the last three years.

CASE SUMMARIES

Case 1.—A. G. (Pkd. 38434), a 26-year-old male, was admitted August 8, 1946, with acute appendicitis and rupture of the appendix. Circulatory and respiratory status were satisfactory. Temperature, 99.6° F., pulse 100, blood pressure 120/70.

Appendectomy was performed, following anesthesia with pentothal sodium (0.5 Gm.), followed by cyclopropane and oxygen, and 160 units of "Intocostrin." Anesthesia was uncomplicated except for profuse sweating. No fluids were given intravenously before or during operation. Immediately postoperatively, a solution of 5 per cent dextrose in

* Read before the American Surgical Association, Colorado Springs, Colorado, April 19, 1950.

distilled water containing 3 Gm. sodium sulfadiazine per liter was started intravenously, but was discontinued shortly thereafter when the patient suffered a chill.

Postoperative course. Three hours after the chill began he was sweating profusely, and was moderately cyanotic; pulse rate 140, blood pressure 80/30, temperature 99.8° by mouth. One liter of 5 per cent dextrose in distilled water was given slowly intravenously.

Six hours after the chill his rectal temperature reached 106°, pulse rate more than 180, and blood pressure was 69/30. Respirations were 38 per minute and labored. He was cyanotic and sweating profusely.

Physical examination of chest, on August 9, revealed: right inspiratory lag; diminished expansion of right chest, with an expiratory position of the right hemithorax; distant breath sounds with patches of dullness over the right chest. On the same date, roentgen examination revealed: upper two thirds of right lung clear; base of right lung somewhat hazy, probably the result of technical variation rather than intrapulmonary disease. Bronchoscopic examination at this time yielded moderate amount of thick secretion in both main bronchi, more especially in the right one. Following this examination a loose, rattling cough developed, productive of only small amounts of thick, clear sputum.

Oxygen was administered through an oro-nasal mask, but cyanosis persisted. One and a half liters of 5 per cent glucose in normal saline were given slowly, intravenously. Cold packs and rectally administered aspirin were employed to lower his fever. Five hours after bronchoscopy his temperature was still 103° F., pulse rate was 140, respiration 26, and blood pressure 80/40. Cyanosis had disappeared and he was breathing easily.

Twelve hours later the oxygen was discontinued, and cyanosis did not reappear. He had no fever, pulse rate had fallen to 112, respiratory rate was normal, but blood pressure was still only 84/50. The right chest still lagged during inspiration, and dullness and bronchial sounds were found over large areas of the whole right hemithorax. No evidence of tracheal deviation or of mediastinal shift was found.

One day later only the chest lag remained and he felt well. Blood pressure was then 100/60.

Roentgenogram of the chest on August 12 indicated no evidence of atelectasis, tuberculosis or pneumonia. Haziness at the base of the right lung had disappeared.

Case 2.—J. V. (pkd. W51872), a 59-year-old woman, was admitted October 6, 1947, suffering from diabetes mellitus and meningococcal infection. There was a 3-week history of weakness, dizziness, polydipsia, polyuria, and anorexia, progressing to coma 16 hours before admission, with disorientation for 12 hours preceding the coma.

Physical examination. Her rectal temperature was 104.4°. The skin was dry and cool and without turgor; breathing was shallow, rapid (48 per minute), and grunting. The lungs were clear to auscultation; chest expansion was free and equal. Blood pressure was imperceptible to auscultation; peripheral pulse was 120 per minute and difficult to palpate. The point of maximum intensity of the cardiac beat was diffuse and outside the mid-clavicular line. The abdomen was distended and tympanitic. There was no roentgen ray evidence of parenchymatous infiltration in either lung field. There was some haziness of both costophrenic sinuses. Petechiae covered most of the body, and there were many large purplish indurated areas over the lower extremities.

During the first 12 hours the urine output was 400 ml., and the fluid administered totaled 10,450 ml., of which 4450 ml. were of a balanced salt solution, and the remainder was of 5 per cent dextrose in distilled water. Antibiotics and insulin were also given. During this period the blood pressure reached 120/90, and the patient became rational. The carbon dioxide combining power reached 50.4 volumes per 100 of plasma, and the blood sugar fell to 484 mg. per 100 cc.

During the next 24 hours she became comatose again, and her blood pressure was not obtainable. She received 2750 ml. plasma, and 4000 ml. glucose in distilled water.

Urine output during this time was 660 ml. Respiratory rate rose to 36 per minute, and breathing was abdominal in character and labored. Breath sounds were absent over much of both lung fields. Tidal air was very small. Cyanosis was definite. Roentgen ray examination of the chest showed elevations of both hemidiaphragms without evidence of pneumonia, pleural effusion or other abnormalities.

On the third hospital day she again became lucid, but later while being bathed, she suddenly ceased breathing, and a peripheral pulse was not obtainable. Following an intracardiac injection of 0.5 mg. epinephrine and artificial respiration by intermittent positive pressure oxygen by mask, she began breathing again, and the pulse was palpable. She remained comatose throughout the remainder of her hospital course. Fluid therapy during the third hospital day was 800 ml. 5 per cent dextrose in distilled water, intravenously, and 1000 ml. of 5 per cent dextrose in distilled water by clysis. She excreted 100 ml. of urine.

On the fourth hospital day she was given 500 ml. of blood intra-arterially, and the blood pressure reached 105/70 and remained elevated while an additional 1000 ml. of blood were given intravenously. Desoxycorticosterone was also given. Urine output for the fourth day was 375 ml.

Digitalization was carried out on the fifth hospital day, using "Purodigin," 1.2 mg. intravenously. The systolic blood pressure remained between 85 and 116, while the diastolic was 60 to 80 mm. of mercury. Respirations were rapid and shallow, and the pattern was not changed by caffeine sodium benzoate, intravenously, or by carbon dioxide inhalations. Fluids for the fifth day consisted of 2000 ml. of 5 per cent dextrose in distilled water intravenously, and 2400 ml. of 5 per cent dextrose in distilled water by clysis. She excreted 300 ml. of urine.

Her physiologic status was apparently unchanged on the sixth hospital day, and her fluid intake consisted of 1000 ml. of 5 per cent dextrose in distilled water by clysis, and 1000 ml. of a balanced salt solution by clysis. Her urine output was 300 ml.

On the seventh hospital day there was an almost continuous flow of brown, liquid feces. Persistent cyanosis was present. Breathing was very rapid and labored. Distant bronchial breathing was present over both lower lung fields. There was dullness to percussion over both lower lung fields, and coarse, fine, persistent râles throughout the lungs. Respiration was assisted by positive pressure oxygen. Roentgen ray examination demonstrated atelectasis in the right lung base, posteriorly, and probable pleural effusion on the right. Respiratory arrest took place, followed shortly by cardiac standstill. On this day she had received 1000 ml. of a balanced salt solution by clysis, and an uncharted total of feedings by stomach tube.

Postmortem findings. Grossly bilateral massive atelectasis was present. Mucopurulent material was found in the trachea and in the primary bronchi. This material was soft and easily detached from the air passages. The right lung weighed 400 Gm. and was considerably collapsed. The parenchyma of the right lower and right upper lobes was firm in consistency and of a dark purplish color. The cut surfaces were deep reddish purple in color and of homogeneous quality throughout. The parenchyma was firm, rubbery in consistency, and fluid was not expressible. The middle lobe was crepitant and of a salmon-pink color. The left lung weighed 400 Gm. and showed the same general appearance as the right lobes. Extensive atelectasis with moderate intracapillary congestion was discovered histologically. No intra-alveolar hemorrhages, no pulmonary edema, no emphysema, and no bronchiolar plugging could be found.

Case 3.—H. J. (Pkd. 63178), a 36-year-old man was admitted October 1, 1948, suffering from a shotgun wound of the right buttock with perforation of the rectum and sigmoid colon, retroperitoneal hematoma, and primary syphilis. He was in profound peripheral circulatory failure. The blood pressure was unobtainable; 750 ml. of plasma and 500 ml. of blood were administered intravenously. Following this, his blood pressure rose to 110/60. However, he experienced a chill during the administration of the

second bottle of plasma after 250 ml. were injected. When anesthesia was begun his blood pressure was 115/50, his pulse was 88 per minute, and he was fully conscious.

Pentothal sodium with nitrous oxide-oxygen induction was used for anesthesia. This was followed by endotracheal ether-oxygen maintenance. The laceration of the sigmoid was closed, and proximal sigmoid colostomy, debridement of the wound of the buttocks, and a posterior incision to drain the perirectal space were accomplished. During the operation 1400 ml. of blood were given intravenously. Blood pressure at this time was 90/45, pulse 100, and respirations 36.

Postoperative fluid therapy was as follows:

During first 12 hours, 1000 ml. blood and 1000 ml. 5 per cent glucose in water were given. Blood pressure was 60/40, pulse 120, and respiration accelerated up to 52 per minute.

At 15 hours, 500 ml. blood were given. Blood pressure was 16/0, pulse 132.
At 18 hours, 500 ml. plasma were given. Blood pressure was 68/40.
At 20 hours, 500 ml. blood were given. Blood pressure was 68/40.
At 27 hours, 500 ml. blood were given. Blood pressure was 60/40.
At 28 hours, 500 ml. blood were given. Blood pressure was 76/50.

On October 3 he showed resistant cyanosis. A roentgen ray film of the chest showed an area of infiltration behind the cardiac silhouette on the left. This had the appearance of pneumonia, with some atelectasis. The right base, the site of the clinical findings, was clear. The following excerpt from the resident's note describes his subsequent course, approximately 36 hours postoperative'y.

"October 3, 7 P.M. Pulse 120, temperature 98² axillary. Venous distention is prominent in neck veins. Marked expiratory effort is present. Paradoxical pulse = 10 mm. mercury. P_2 is louder than A_2, and P_2 has a slapping quality. There are crepitant râles in right lower lung field. Median basilic venous pressure = 170 mm. saline. P.M.I. is in anterior axillary line and left cardiac border has advanced 2-3 cm. laterally to percussion. Four ml. Cedilanid given intravenously. This dose to be repeated in 4 hours. Patient has passed no urine since operation, so an indwelling catheter was inserted and about 200 ml. dark brown urine was obtained.

"October 3, 12:00 M. Blood pressure 110/60, pulse 72. Respiration of normal depth and no expiratory effort. No Cedilanid to be given tonight. He has improved remarkably.

"October 4, 1:05 A.M. Death occurred suddenly and without any unusual event. Respirations ceased first, then the pulse and heart beat ceased in about two minutes. Ten minutes prior to death, the nurse checked blood pressure = 104/50, and pulse = 72."

Postmortem findings. Large gunshot wound of right buttocks, extending into the pelvis; elevation of the hemidiaphragms to the fifth interspaces. Weight of right lung 900 Gm. (weight of left lung not recorded). Diffusely red pulmonary parenchyma with slate-blue color of dependant portions; the intrapulmonary and the right main bronchi were obstructed with clotted blood. A very hemorrhagic mass of pulmonary tissue was found in the lower posterior lobular segments of the right lung. This looked like an infarct, but obstruction to the respective pulmonary arterial segments could not be found. The left lung was grossly similar to the right. Only the anterior medial segments of both lungs contained any air. Edema fluid could be expressed from scattered areas on the cut surfaces. (See Figure 9A.)

Microscopically all sections of the lungs showed intense capillary congestion, massive intra-alveolar hemorrhage, patchy areas of pulmonary edema superimposed upon the congestion and hemorrhage, and incomplete expansion of the pulmonary parenchyma.

Case 4.—J. G. (Pkd. W43543), a 45-year-old man was admitted January 5, 1947, with a diagnosis of perforation of a jejunal ulcer seven years after the performance of a posterior gastro-enterostomy. His respiratory rate was 20, and no signs of

peripheral circulatory failure were present. All pulmonary and cardiac auscultatory signs were normal; 1000 ml. of 5 per cent dextrose in water were administered intravenously.

Omental closure of the perforation was done, using pentothal sodium (0.5 Gm.) anesthesia induction, followed by cyclopropane-oxygen and 80 units of "curare." During the operation 400 ml. of 5 per cent dextrose in water were given intravenously.

For the first two postoperative days he felt well and had no fever. Two liters of 5 per cent dextrose in water and one liter of 5 per cent dextrose in saline were given intravenously each day.

At 1:25 A.M. on the third postoperative day, while he was receiving a rapid intravenous infusion of 5 per cent dextrose in saline (600 ml. in 40 minutes) he complained of nausea and suffered unproductive retching. The infusion was stopped and he quieted and slept. One hour later he was found pulseless. Oxygen was started, Coramine and adrenalin were injected intramuscularly, and 1000 ml. of plasma and 500 ml. of blood were infused intravenously. His mouth temperature then rose to 105°, his pulse to 120-140 per minute, and his respirations to 32. An ashen cyanosis appeared, and he became disoriented. His blood pressure was recorded at $\frac{40\text{-}60}{30\text{-}40}$ for the next 48 hours. Oxygen was administered through a mask and later by a tent. Examination of the chest 15 hours after the onset of trouble showed right inspiratory lag, forceful, grunting expiratory movements, multiple areas of dullness and distant bronchial breathing over the right middle and lower lobes. The heart sounds were distant. No râles could be heard. No signs of a mediastinal shift were elicited, and the tracheal position was normal. The presence of a "massive collapse" of the right middle and lower lobes was suspected by one examiner but not by others. There were no peripheral signs of congestive cardiac failure. No roentgenographic evidence of atelectasis or other significant abnormality of the chest was observed.

The following day, 2 ml. of "Cedilanid" were injected intravenously, and his blood pressure rose. On January 11, respiratory rate was 24, and no cyanosis was present. Examination of chest was as on January 9. However, the signs of pulmonary trouble spread gradually. The areas of dullness and damped bronchial breathing over the right lower lobe coalesced, and dullness appeared over the right upper and the left lower lobes during the following days. Persistent basilar and right axillary râles were noted. Cyanosis returned on January 14 and persisted, and the patient continued to be disoriented. Respiratory rate was 30 per minute. He also became oliguric and azotemic. Five days after the onset of trouble, a bronchoscope was passed and small amounts of a thin, watery, blood-stained fluid were seen in and removed from the major bronchi. The bronchi were unobstructed. The bronchial mucosa was boggy and red. Considerable expiratory bulging of the bronchi and trachea were noted. After removal of the fluid, a foamy fluid flowed into the main air passages. He died an asphyxial death 6 days after the "infusion reaction." A film of the chest taken on the day of death with a mobile unit showed an extensive infiltration involving practically the entire right lung field, which was slightly less dense around the periphery. On the left a dense infiltration extending from the hilum which does not extend to the periphery, was seen. These changes were considered to be due chiefly to pulmonary edema, although the possibility of some bronchopneumonia existed.

Postmortem findings. The right lung weighed 730 Gm.; it was reddish-grey in color. The upper lobe was firmer than the remainder of the lung; it was not crepitant. The cut section of this lobe was reddish-grey in color and had a homogeneous fleshy appearance. A moderate amount of thin reddish fluid was expressible from the cut surface. The middle and lower lobes were pinkish-grey and were moderately crepitant. The intrapulmonary bronchi of all lobes were hyperemic and contained some thick mucinous yellow material. The pulmonary arteries were patent. The left lung weighed

590 Gm., and the major portion of the upper lobe and all of the lower lobe were non-crepitant. The non-crepitant areas were reddish-grey, and after sectioning a small amount of thick reddish fluid could be expressed from the cut surface. The intrapulmonary bronchi were hyperemic and contained a thick yellow mucinous material. The pulmonary arterial branches were normal. The heart was normal except for a number of fine fibrinous strands which connected the visceral and parietal pericardial surfaces. The epicardial surface was reddish and had a granular appearance.

Microscopically the sections of the lungs showed two types of abnormality. One was characterized by complete atelectasis with congestion of pulmonary capillaries, small, widely separated areas of intra-alveolar hemorrhage, no edema, and filling of the bronchioles with disintegrating and disintegrated (ghosts) red blood cells. The other was marked by incomplete collapse of alveoli, widespread intra-alveolar hemorrhages, innumerable heart-failure cells, intense capillary congestion, small patches of edema, and filling of the bronchioles with red cells and polymorphonuclear leukocytes. No bacterial colonies could be found and the alveoli were free of leukocytes.

Case 5.—R. F. (Pkd. 64224), a 62-year-old man, was admitted November 8, 1948, suffering from a perforated carcinomatous gastric ulcer. Blood pressure was 150/74, pulse 120, and respiration 18. There were no signs of peripheral circulatory failure, or of congestive heart failure. A_2 was equal to P_2. There was moderate emphysema, and no râles. Lung fields were clear to percussion and auscultation. Roentgen ray film of the chest together with AP and transverse films of the abdomen showed air under the right diaphragmatic leaf with an underlying fluid level. Infiltration, considered to represent atelectasis, in the adjacent portion of the right lung was detected. No preoperative fluid was given.

Omental closure of the perforation was performed under nitrous oxide-oxygen-ether anesthesia given by intratracheal tube. During the operation 500 ml. of blood were given intravenously.

During the anesthetic recovery period signs of peripheral circulatory failure appeared and 500 ml. of blood and 1000 ml. of lactated Ringer's solution were given in 3 hours. Subsequently, one liter of 10 per cent glucose in saline and one liter of 10 per cent glucose in water were given intravenously. Total intravenous fluid input for the day of operation was 5 liters, and no urine was passed.

The next day his temperature and pulse had fallen toward normal levels, and all signs of peripheral circulatory failure had disappeared. Following the administration of one liter of Hartmann's solution and 2 liters of 5 per cent glucose in water, subcutaneously, he developed labored breathing and tachypnea. Visible, forceful expiratory efforts were being made. Venous pressure was elevated and expiratory wheezes and râles were heard over the lower pulmonary fields bilaterally. No peripheral edema was present. He was placed in a sitting position and the fluid administration stopped. Breathing became less labored. Digitoxin (0.3 mg.) was given intravenously. He passed no urine this day.

The respiratory difficulties persisted and progressed slowly. Two liters of fluid were given intravenously for the 3 subsequent days, and 225 ml. of urine were passed. On November 11 respirations were labored, 20 per minute, and were marked by bilateral basilar expiratory wheezes. Numerous fine crackles and posttussive râles up to the fifth dorsal spine were heard. Dullness to percussion was present over both lower lung fields. The pulmonary arterial second sound was louder than the aortic sound. Roentgen ray showed persistence of the atelectasis on the right and a rather homogeneous area involving both lower lung fields. The latter was considered to be due to hypostasis.

An hyperemic and edematous bronchial mucosa was all that was seen at the time of bronchoscopy. Because of the failure to find bronchial obstruction while he showed signs of a rising right diaphragm, tachycardia, and rising temperature, the right sub-

phrenic spaces were explored under local anesthesia, and found normal. Death occurred 4 hours later.

Postmortem findings. The lungs filled 80 to 85 per cent of the opened chest. The right lung weighed 775 Gm. The right upper and lower lobes were deep reddish brown and firm in entirety. The middle lobe was normal. No bronchial obstruction was found. The entire left lung simulated the right upper and lower lobes, and contained little air; considerable hemorrhagic material was expressible therefrom after section. The pulmonary arteries were all patent. An intense capillary congestion with massive intra-alveolar hemorrhage, minimal pulmonary edema, and incomplete expansion of the alveoli were observed microscopically in the section taken from the right lower lobe. The right upper lobe section was similar to that taken from the right lower, except that more edema was present. The section taken from the right middle lobe showed only capillary congestion.

Case 6.—A. M. (Pkd. 65115), a 52-year-old man, was admitted December 16, 1948, suffering from gunshot wounds of the pharynx, mandible, colon, and liver. He had mild peripheral circulatory failure and was conscious. Blood pressure was 100/72, pulse 120, respiration 28. Peripheral pulses were of good volume. Respiration was somewhat labored. No râles were heard. Point of maximum cardiac impulse was at the midclavicular line in the fifth left intercostal space. Five hundred ml. of plasma and 250 ml. of blood were given intravenously.

At operation, a colostomy followed by tracheotomy were performed. The anesthetic consisted of pentothal sodium, 0.4 Gm., and 80 units of d-Tubocurarine followed by tracheal intubation and endotracheal semi-closed ether vapor anesthesia—120 ml. of ether were used. Bronchoscopic examination was performed just before the tracheotomy. The bronchial tree was free of blood and secretions. Blood pressure was well maintained until the termination of the operative procedures, and then it fell precipitously to 80/60 following bronchoscopy; 750 ml. of blood were given intravenously during the operation.

Because of the acute hypotension, 500 ml. of blood were given immediately after the termination of the operation. The blood pressure rose to 120/80, and the pulse rate fell to 120, but the minute respiratory rate increased to 34-40, with intervals of Biot and Cheyne-Stokes breathing. Ten hours postoperatively râles were heard over the whole right thoracic cage, and the point of maximum cardiac impulse was found to have shifted to the mid-axillary line without shift of the trachea or mediastinal structures. Breath sounds were transmitted well through the thoracic cage. Digitalization was begun with "Crystodigin," 0.4 mg., intravenously. His respiration remained shallow, labored and rapid. Periods of apnea lasting 30 seconds or more began, and his blood pressure began to fall. One-half liter of blood was then given and his blood pressure rose to 150/100. Five hundred ml. of plasma and a liter of 10 per cent glucose in water were then given (500 blood, 500 plasma, 1000 water in four hours) and the blood pressure fell steadily, the pulse rate increased, and the respiratory rate remained about 40. More "Crystodigin" (0.4 mg.) was administered intravenously and the blood pressure rose to 170/110. Later the blood pressure again fell precipitously and after the injection of another one-half liter of blood it disappeared and could not be determined before his death 8 hours later. Breathing became very labored, deep, and remained rapid. Repeated tracheal aspiration throughout his postoperative life removed very little. Consciousness did not return at any time after the anesthesia was begun. Oxygen was administered via an oro-nasal Boothby-Lovelace mask throughout the postoperative period.

Postmortem Findings. The lungs weighed 1755 Gm. (his liver weighed 1825 Gm.). Only the anterior superior surfaces of the upper lobes contained air. The remaining portions were dark red and contained practically no air. A small amount of bloody-frothy fluid was expressible from the cut surface. The smaller bronchi were hyperemic. The major bronchi were not obstructed. Microscopically, all sections of the lungs showed intense intra-alveolar hemorrhage and capillary congestion, patchy pulmonary

edema, and a few areas of intense capillary congestion without intra-alveolar hemorrhages or edema. Expansion was incomplete in all segments. No bronchial plugs were seen. (See Figure 8A.)

Case 7.—W. C. L. (Pkd. W51671), a 52-year-old man, was admitted September 17, 1947, suffering from extrahepatic obstructive jaundice due to stone, and chronic cholecystitis with cholelithiasis. His blood pressure was 134/77, and pulse 89. There was mild emphysema. No preoperative fluids were administered.

Operation consisted of cholecystectomy and choledochostomy. Anesthesia was induced by sodium pentothal followed by cyclopropane, followed by ethylene, followed by ether in a closed circuit. Blood pressure and pulse were normal throughout the operative procedure. Post-anesthetic reaction was rapid and accompanied by excitement, and 500 ml. of 5 per cent glucose in water and 500 ml. of blood were given intravenously during the operation.

All went well for 4 days postoperatively, and, except for a mild nausea, progress was satisfactory. Because of the nausea intravenous fluids were given daily as follows:

Day of operation: 1300 ml. of 10 per cent dextrose in water; first postoperative day: 2000 ml. of 10 per cent dextrose in water; second postoperative day: 3000 ml. of 10 per cent dextrose in water; third postoperative day: 3000 ml. of 10 per cent dextrose in water; fourth postoperative day: 200 ml. of 10 per cent dextrose in water.

At 9:30 A.M. on the fourth postoperative day, while receiving the first 200 ml. of a projected dose of 2.5 liters of 10 per cent glucose in distilled water, he developed a chill. The infusion was discontinued, and the chill stopped soon thereafter. By 11:15 A.M. his mouth temperature had risen from 99° to 100.6°, his pulse rate was 150, and his respiratory rate was 40 per minute. At this time there was an episode of projectile vomiting, following which he complained of a feeling of substernal pressure. A peripheral pulse was not palpable. He became extremely dyspneic and his skin was ashen-grey. One and one-half hours later his skin was cool and dry, while his rectal temperature stood at 106.6° F. No blood pressure reading was obtainable. The right lung transmitted breath sounds poorly, but no mediastinal or tracheal shift could be detected. There was slight dullness over the right hemithorax. Roentgenogram revealed no evidence of atelectasis or other significant abnormality involving the chest. Oxygen was given by mask and one liter of blood was infused. No relief from the dyspnea and cyanosis was provided by the oxygen. His pulse had re-appeared before the blood transfusion, but thereafter he became pulseless and remained so for 5 hours, when he died.

Postmortem Findings. The lungs filled 70 per cent of the opened chest. They weighed 1135 Gm. and were red and firm throughout. The cut surface did not bleed readily. The anterior portions of the right lung were somewhat crepitant. The left lung was similar to the right lung but was non-crepitant. No pulmonary arterial thrombi or emboli were found. The bronchi were open.

Intra-aleolar hemorrhage, intra-alveolar edema, and intense capillary congestion were the microscopic characteristics of the posterior parts of the right lung. All segments of the left lung showed intense capillary congestion coupled with atelectasis without intra-alveolar hemorrhage or edema. Congestion of the hepatic sinusoids and the adrenal and renal capillaries were also found. A few old subendocardial microscopic infarcts were noted. The large coronary vessels were completely patent.

Case 8.—T. L., H-157-49, a 25-year-old man, was admitted January, 1950, with traumatic rupture of the third portion of the duodenum, pancreatic fat necrosis, necrosis of the inferior portion of the right rectus muscle, and retroperitoneal hemorrhage. His apical pulse was 180, radial pulse 90, and blood pressure 60/0. One liter of Hartmann's solution, 750 ml. of irradiated plasma, and 1000 ml. of blood were given intravenously.

At operation closure of the duodenum, and drainage of the left duodenal fossa and the space of Retzius were done and 500 ml. of blood were given during the operative procedure.

A continuous intravenous drip of blood was begun with the operation and continued for 11 hours. At 3:30 A.M., 5 hours postoperatively, his blood pressure was 96/70, his pulse was 132, and his respiratory rate was 42. By 8:00 A.M. (11 hours after the operation) he had received an additional two liters of blood. At 8:00 A.M. his blood pressure was unobtainable, and the rate of injection of the blood was increased. One liter of blood flowed in during the following hour, and his blood pressure rose to 85/0. The infusion was continued with 750 ml. of Hartmann's solution and 750 ml. of 10 per cent dextrose in water, and by 3:00 P.M. his blood pressure had risen to 125/80. His pulse rate had increased to 136 and his respiratory rate to 54 per minute and a deep resistant cyanosis had appeared. The blood pressure again began to fall and another liter of blood was injected intravenously, and the blood pressure became unobtainable while his respiratory rate climbed to 62 per minute. He died one-half hour later. Breathing was labored throughout the postoperative period. No râles were heard. With the repeated transfusions the red blood cell count rose from 5.79 million to 8.82 million and the hemoglobin climbed from 18.5 Gm./100 ml. to 24 Gm./100 ml.

Postmortem Findings. (1) The right lung weighed 550 Gm. and the left lung 600 Gm. Both lungs were dark blue and airless. They felt solid and abundant blood could be expressed from their cut surfaces. The bronchi were filled with a hemorrhagic, fluid, frothy material. The pulmonary arteries were patent. One and one-half liters of a hemorrhagic fluid were present in each thoracic cavity. (2) The heart was normal. (3) There was extensive retroperitoneal edema with some hemorrhage. Microscopic findings consisted of an intense capillary congestion, incomplete alveolar expansion, and diffuse intra-alveolar hemorrhage characterized the pulmonary microscopic picture. No pulmonary edema existed.

The signs associated with the development of the congestion, intra-alveolar hemorrhage, and incomplete expansion of the lungs are listed in Table I. Some of the possible causes of the trouble may be adjudged from clinical correlations (see Table II). Physical injury, excessive fluid administration, anaphylactoid reactions, pre-existing shock, and rapidity of intravenous infusion appear to be contributory factors. More will be said about them in the discussion.

Thus far the attempts that have been made to reverse the process have been unsuccessful. Only one young, strong man recovered. Because of the discovery of cardio-pulmonary signs suggestive of congestive cardiac failure, preparations of digitalis acceptable for rapid digitalization were given to five of the eight; all of them died. Humidified oxygen was administered through an oro-nasal mask to everyone, but it did not clear the cyanosis and it did not save them. Phlebotomy was not attempted because it had been tried five years before and failed. Bronchoscopic aspiration was performed on five of the eight, and one of them recovered. However, the recovery was not dramatic, and a bronchial obstruction was not found; therefore it is possible that the bronchoscopy had little to do with his recovery. Blind tracheal aspiration was employed in two of the three others. Little fluid was removed, and they died. The breathing of oxygen under positive pressure was used in one instance (J.V.); it served to prolong her life but did not effect reversal of the process. Frequent turning, coughing, encouragement of deep breathing, and the inhalation of five per cent carbon dioxide in oxygen were tried.

DISCUSSION

Congestive atelectasis was suggested by E. E. Muirhead as the descriptive term best fitting the macroscopic and microscopic appearance of the lungs of these people. At the time he made the suggestion, he was not aware of the fact that Fegler and Banister had employed it earlier[10] (see introduction). It is remarkable that the diagnostic criteria adopted by Fegler and Banister, and Muirhead are practically identical.

TABLE I

Case	A.G.	J.V.	H.J.	J.G.	R.F.	A.M.	W.C.L.	T.L.
Respiratory Signs								
Labored breathing	+	+	+	+	+	+	+	–
Tachypnea	+	+	+	+	+	+	+	+
Accentuation of expiratory effort	+	–	+	+	+	–	–	–
Pulmonary Signs								
Dullness	+	+	–	+	+	O	O	–
Diminished transmission of breath sounds	+	+	–	+	O	O	+	–
Râles	O early	+	+	O	+	+	O	O
Mediastinal cardiac and tracheal shift	O	O	O	O	O	O	O	–
O_2 Therapy used	+	+	+	+	+	+	+	+
Cyanosis not alleviated by the administration of oxygen	+	+	–	+	–	+	+	+
Cardiovascular Signs								
Hypotension	+	+	+	+	O	+	+	+
Tachycardia	+	+	+	+	+	+	+	+
Increased venous pressure	–	–	+	–	+	–	–	–
Enlargement of cardiac areas	–	+	+	–	–	+	–	–
Roentgenographic abnormality at time of earliest significant signs of pulmonary trouble	Haziness of right base	Elevation of hemidiaphragms only	No signs on the side of maximum trouble	Normal chest	Atelectasis lower lobe right homogeneous density over lower lung fields		Normal chest	
Temperature response	106° F (R)	–	O	103° F. (O)	102.6° F. (O)	105° F. (R)	106.6° F. (R)	102° F.
Outcome	Recovery	death	death	death	death	death	death	death

Legend: + =present; O =absent, and – =indeterminate from the record at the time of notation of the other listed signs.

Gross and microscopic descriptions of the phenomenon are numerous. Some are to be found in descriptions of "massive collapse of the lung."[2, 5, 17] The pathologic report of an instance of acute bilateral (non-obstructive) atelectasis by Symmers, Miles and McGrath, quoted by Bergamini and Shepard[2] is a good example:

"At autopsy—left lung collapsed; right lung partially collapsed, moderately engorged; no food in bronchi; tongue natural. Fairly well-marked laryngeal oedema.

The epiglottis was peculiar in shape; no obstruction by food. Heart and abdominal organs normal.

"Histological findings reported as follows by Doctors Symmers, Miles and McGrath: 'Examination of microscopic preparations from the collapsed pulmonary lobes reveals a tissue which it is difficult to recognize as lung, resembling rather a solid organ. This appearance is found to be due to complete atelectasis of the pulmonary alveoli, the epithelical cells of which lie closely packed together, having lost entirely their normal alveolar arrangement. The individual cells are swollen, certain of them being obviously hydropic, and the cell outlines are rather indistinct. The bronchioles are also collapsed for the most part, many of them being represented merely by circular clumps of cuboidal cells. The capillaries, arterioles and venules, on the other hand, are all uniformly dilated and filled with blood, producing almost an angiomatous appearance in certain areas. This constitutes the most characteristic feature of the histology of the condition.'"

TABLE II

Case	A.G.	J.V.	H.J.	J.G.	R.F.	A.M.	W.C.L.	T.L.
Pre-existing hypotension or shock	no	yes	yes	no	no	slight	no	yes
Physical injury (operative included)	yes	no	yes	yes	yes	yes	yes	yes
Rapid intravenous injection of fluid	no	yes	no	yes	no	yes	no	yes
"Excessive" fluid given								
a. Blood	no	no	yes	no	no	yes	no	yes
b. Plasma	no	no	no	no	no	no	no	no
c. Saline	no	yes	no	no	yes	no	yes	no
d. Glucose in water	no	yes	no	no	yes	no	yes	no
Pre-existing extracellular fluid deficit	no	yes	no	no	no	no	no	yes
Anaphylactoid* reactions to the parenteral fluids	yes (glucose) Na-sulfadiazine	no	yes to plasma	yes to glucose in saline	no	no	yes to glucose in water	no
Pre-existing heart disease	no	no	no	no	no	no	old microscopic myocardial infarcts	no
Pre-existing pulmonary disease	no	no	no	no	yes	no	no	no
Hemo-concentration	no	no	no	no	no	—	—	yes
Hemo-dilution	no	yes	yes	yes	yes	—	—	no

* No living bacteria were found in any of the fluids producing the reaction.

Other descriptions of congestive atelectasis are to be found in discussions of the pathologic changes associated with rapid decompression,[4] and in the organ—descriptive literature of shock,[16] blast injury,[21] burns,[15] and the excessive transfusion of blood.[13]

The symptoms and signs of congestive atelectasis differ from those associated with obstructive atelectasis only in a few respects. The congestive type is attended by a cyanosis that is generally deeper and does not clear as readily when oxygen is breathed. The mediastinal structures do not shift appreciably with congestive atelectasis, but do with the obstructive. However, one cannot be sure about this because the congestive process was bilateral in everyone examined after death and therefore a mediastinal shift would not be as likely to occur as it would had the involvement been unilateral. The presence, location, and extent of obstructive atelectasis are fairly determinable with roentgen rays[1, 19, 20] but the determination of the presence and extent of congestive

atelectasis cannot be made early with them. In other words, obstructive atelectasis produces organic pulmonary changes detectable with roentgen rays, and early congestive atelectasis does not. In this series there is no correlation between the roentgenologic, the physical, and the postmortem examinations. The proved extent of pulmonary involvement was greater than the physical signs indicated, and the physical signs were more indicative of the extent of the process than the roentgen signs were.

The congestive and the obstructive types of atelectasis differ also in respect to the effectiveness of bronchoscopic and tracheal aspirations in their treatment; bronchoscopic and tracheal aspirations are very effective therapeutic measures for the latter type[12, 18] but apparently have little therapeutic effectiveness for the former.

The physical signs and symptoms of congestive atelectasis are sufficiently similar to those of congestive cardiac failure[19] to suggest that left heart failure might be its cause. If this were true, digitalization should have saved some of the five individuals to whom preparations of digitalis were given. One (H.J.) showed a dramatic, immediate response to Cedilanid. His blood pressure rose and his pulse and respiratory rates fell to normal within five hours —but he died soon thereafter with his alveoli and bronchi filled with blood. Digitalization was attended in two others (J.G. and A.M.) by a temporary return of blood pressure toward normal, but it had no appreciable effect upon the respiratory difficulties or the pulse rate, and they soon died.

It might also be said that congestive atelectasis is only one of the organic manifestations of shock.[16] As far as available experimental evidence is concerned that is not any more likely than the possibilities that it might be an attendant physiologic response or a cause of shock under certain circumstances.

These questions cannot be solved without recourse to active experimentation. Two exploratory approaches have been made. The first entailed the study of the effects of the infusion of fluids at rapid rates into normal dogs lightly anesthetized with sodium pentobarbital and into some suffering from "tourniquet shock." The physiologic variables recorded were: tidal air, intrapleural pressure and the jugular venous, pulmonary arterial, left auricular, and systemic arterial pressures.

Tidal air was recorded with a 40 Gm. counter-weighted Hutchinson spirometer of 1000 ml. capacity. The jugular and left atrial pressures were measured with saline manometers of 2 mm. bore that had been calibrated with a mercury manometer. The mean pulmonary and systemic arterial pressures were measured with damped mercury manometers. The chest and pericardium were opened for the insertion of the left atrial cannula and then they were closed. Intrapleural pressure was recorded with a water manometer connected to a special T cannula inserted through an intercostal space. The appearance of the lung was watched through a plexiglass window inserted into the right chest.

Figure 1 illustrates some of the effects of a rapid intravenous infusion of 0.9 per cent saline solution into a lightly anesthetized dog. Soon after the beginning of the infusion, the systemic blood pressure fell 20 mm., and the pulmonary arterial pressure rose eight. At the same time, the jugular venous and left atrial pressures rose two and one millimeters respectively. The infusion was stopped for 15 minutes and the systemic arterial pressure rose and the pulmonary arterial fell and continued to fall for a time after the infusion was started again. Peripheral venous pressure rose steadily, but the left atrial pressure fell and continued to fall even after the pulmonary arterial pressure began its second rise.

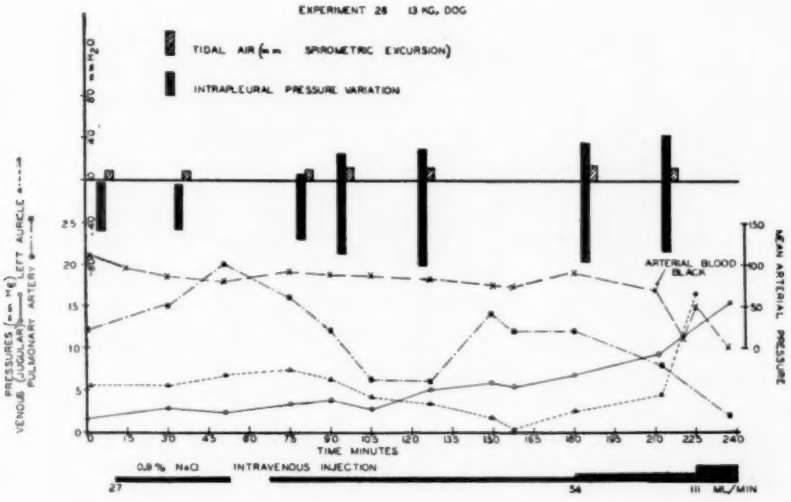


FIG. 1.—The effects of the intravenous infusion of 0.9 per cent solution of sodium chloride upon jugular venous, pulmonary arterial, left atrial, and femoral arterial pressures, tidal air, and intrapleural pressure variations in the anesthetized dog.

Coincident with the decline of the pulmonary arterial and left atrial pressures to levels below those of the pre-injection period, the expiratory intrapleural pressures became positive and the inspiratory became much more negative. At the same time tidal air increased very little. The association of a large increase in respiratory effort, as evidenced by the increase in the change of intrapleural pressure with each breath, with only a slight increment of tidal exchange, denotes an increase in the resistance of the lungs to deformation. In other words, the lungs were becoming stiff.

Thirty minutes before the animal died the rate of consumption of oxygen dropped precipitously (not shown in Figure 1), cyanosis appeared, the systemic and pulmonary arterial pressures fell sharply and the peripheral venous and left atrial pressures rose rapidly. The elevation of venous and left atrial pressures to a level higher than the pulmonary arterial is inexplicable. It is

only seen just before death and after death all pressures quickly reach identical levels. However, before the systemic arterial pressure fell, the lung beneath the observation window became deeply congested and remained so until the animal died.

The lungs were removed after closing the trachea and they barely floated in water. Over 90 per cent of them looked like liver. A cannula was inserted into the trachea and air was introduced through it, and the carnification disappeared. The microscopic examination of a small section of lung removed before the inflation showed intense capillary congestion, intra-alveolar hemorrhage, large areas of incomplete expansion of alveoli, and a little edema (see Figure 2).

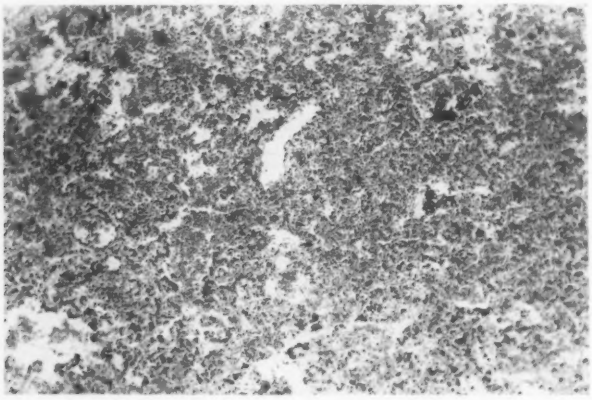


FIG. 2.—Congestive atelectasis produced by the intravenous infusion into an old anesthetized dog of 0.9 per cent sodium chloride at the rate of 45 ml. per minute for 20 minutes.

Other animals given saline rapidly developed fulminant pulmonary edema with practically no congestion. The question "Why do some animals when given saline rapidly die with pulmonary congestion, atelectasis and little edema and others with pulmonary edema without appreciable pulmonary congestion?" cannot be answered. The most significant observation in experiment 26 was the continuous development of pulmonary stiffness *while left atrial pressure was falling*. Therefore, the usual explanation for stiffening of the lungs while saline solution is injected rapidly intravenously, namely, that the left ventricle has been overloaded and fails, is untenable. How can one believe that back-pressure caused by failure of the left heart produces the stiff lung in experiment 26 when the left atrial pressure falls as the lung stiffens?

When the circulation to the hind legs of the animals was cut off for an hour and a half by the application and removal of tourniquets, the responses to the rapid intravenous injection of saline were somewhat different from that shown in Figure 1 (see Figures 3 and 4).

FIG. 3

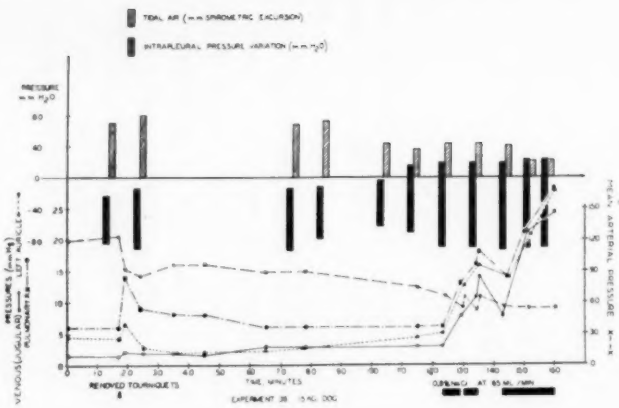
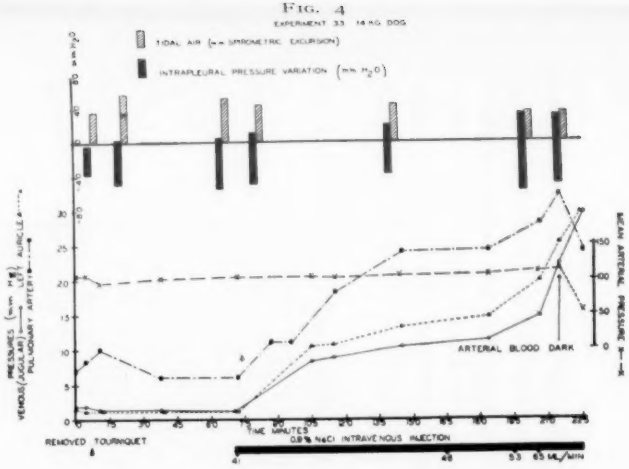
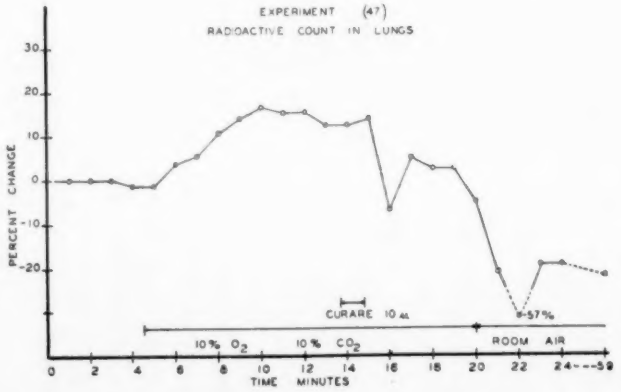


FIG. 4





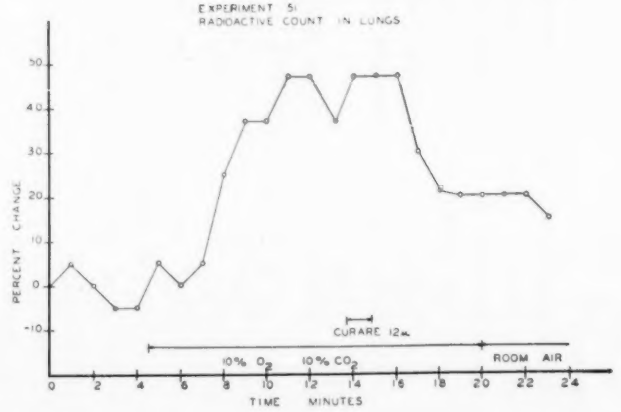


FIG. 5

FIG. 6

FIGS. 3 and 4.—The effect of tourniquet shock and the intravenous infusion of saline solution upon various vascular pressures, tidal air, and intrapleural pressure variations in the anesthetized dog.

FIGS. 5 and 6.—The effect of combined hypercarbia and hypoxia upon pulmonary blood volume of the anesthetized dog, using red blood cells tagged with P^{32}.

The volume of air moved per breath relative to the effort expended in moving it fell and the expiratory intrapleural pressure became positive before the saline was injected. In addition, the lung beneath the window became visibly hyperemic before the infusion was started. After the infusion was started, breathing effort increased quickly and the pulmonary arterial, peripheral venous and left atrial pressures rose rapidly with similar rates of change while systemic arterial pressure which previously had been falling slowly, fell fast during the infusion and rose during the two short periods that the injection was stopped. These pressure changes associated with infusion after tourniquet shock has developed are entirely compatible with backward heart failure.

The sequestration of extracellular fluid in the legs after the removal of the tourniquets is in part the cause of tourniquet shock, and saline solution administered at moderate rates of speed is known to be effective in treating it. However, when it is given very rapidly during tourniquet shock it aggravates the hypotension and presumably induces heart failure.

The observance of hyperemia and a progressive stiffening of the lung as the shock developed before fluid was injected in experiment 36 is indicative, at first thought, that shock is the cause of the pulmonary hyperemia and stiffening. However, the expiratory intrapleural pressure rose quickly toward atmospheric level within six minutes after the removal of the tourniquets, and during experiment 33 (Fig. 4) it was actually positive five minutes after their removal. These observations indicate that at least the lung stiffening is an attendant phenomenon and not the resultant of tourniquet shock. After death, the lungs of dogs 33 and 36 were found to contain air only in anterior segments; the middle and posterior segments showed the macro- and microscopic appearance of congestive atelectasis. Microscopically, the anterior segments were congested and edematous but not atelectatic.

After a year of work, it was realized that the answers which were sought could not quickly be found employing the technics illustrated in Figures 1, 3 and 4 and a more direct approach had to be made.

The changes in the pulmonary blood volume had to be measured in the intact animal. In collaboration with A. Reid, Professor of Biophysics, a fairly direct method was worked out using red blood cells tagged with P^{32}. An aluminum channel, the inner orifice of which was covered with an airtight layer of plastic, was inserted through the chest wall and so adjusted that after the withdrawal of the pneumothorax the inner surface of the channel was constantly in contact with the lung.

A shielded counting tube was attached to the outer end of the channel, making possible a continuous observation of the number of red blood cells within a small segment of lung. Because the emission of beta particles is a function of time, only variation in the volume of blood within the lungs is detectable; changes in the rate of flow alone do not affect the count.

Figures 5, 6 and 7 are examples of consistent changes in the volume of blood in the lung attendant upon controlled asphyxia and hemorrhage. The rapidity with which and the extent to which blood cells collect in the lung following hemorrhage is remarkable. The hemorrhage illustrated in experiment 8 amounted to 175 ml. and was sufficient to lower the mean arterial pressure to 70 mm. of mercury. The rise in pulmonary blood volume attendant upon hemorrhage takes place too quickly to ascribe it to shock.

Controlled asphyxia (10 per cent O_2, and 10 per cent CO_2 in nitrogen) is also attended by speedy and significant increments of blood cells in the lung. Earlier studies of Drinker, Churchill and Ferry[9] failed to demonstrate any significant change in the volume of blood in the lungs with hypercarbia and hypoxia; however the peripheral blood circuit was excluded in their animals.

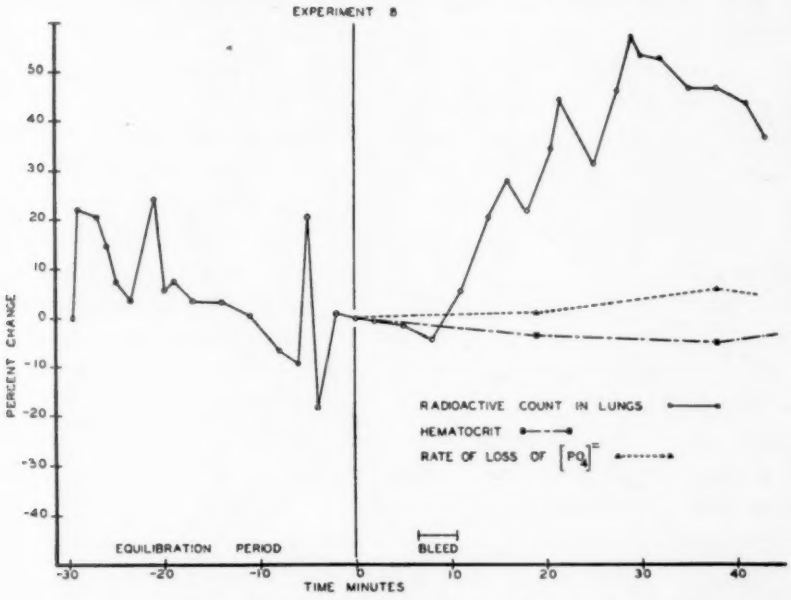


FIG. 7.—Change in the volume of blood in the lungs of the anesthetized dog following a hemorrhage of 175 ml.

The use of radioactive red cells alone does not permit the determination of the changes in the volume of blood in the lungs associated with the intravenous infusion of various fluids with sufficient certainty to permit us to report them now. Random changes in the distribution of P^{32} have been found during the infusion of saline solutions, and because of them methods for the simultaneous determination of the volumes of fluid and the volume of red cells must be developed before one can make accurate determinations of changes in the volume of blood in the lungs associated with the infusion of fluids. The development of such methods now appears to be possible.

It is apparent that the experimental approach has not clarified the etiology of non-decompressive congestive atelectasis. However it has contributed

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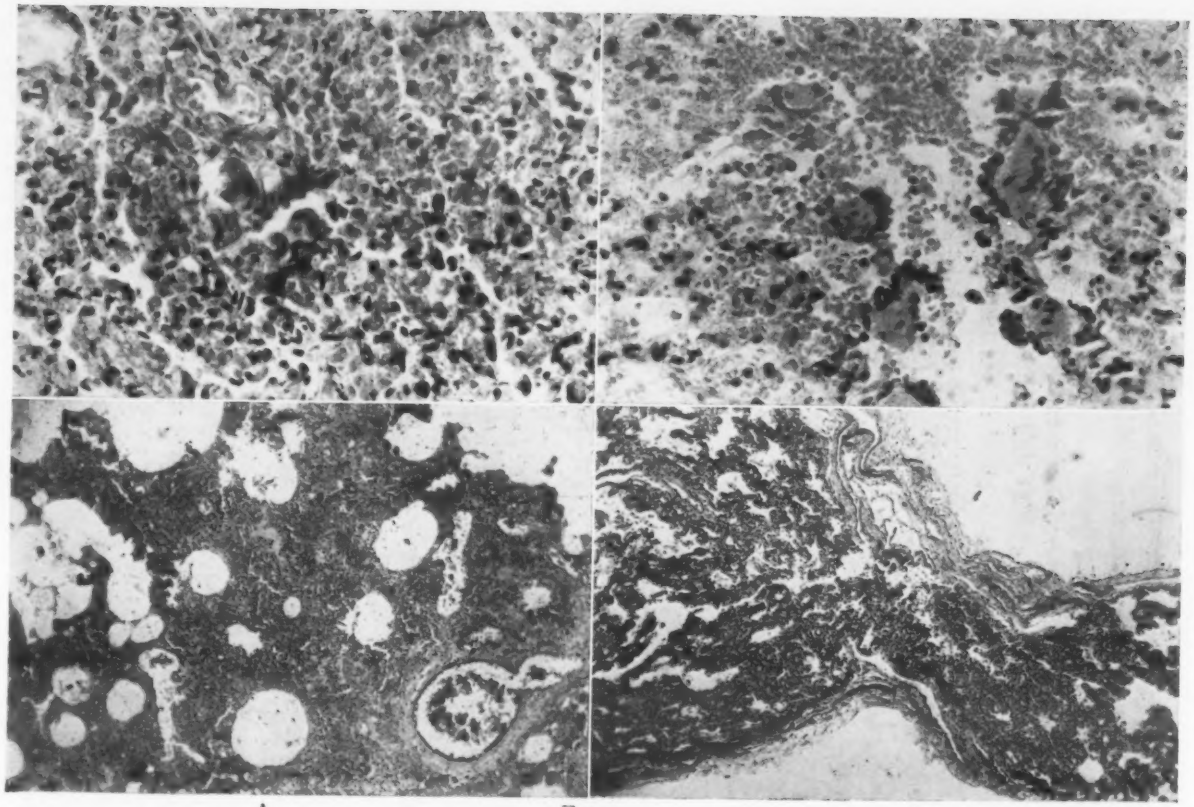
A FIG. 8 B



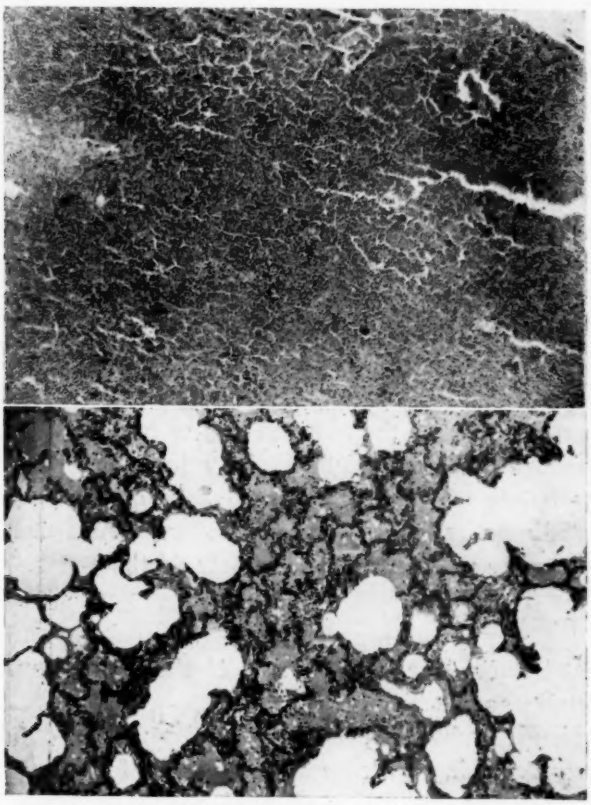
A FIG. 9 B

FIG. 8.—(A) Magnification X 140. Congestive atelectasis. Man (A.M.), case summary in text. (B) Magnification X 225. Congestive atelectasis. Dog (2) anesthetized; saline given intravenously.

FIG. 9.—(A) Magnification X 35. Congestive atelectasis. Man (H.J.), case summary in text. (B) Magnification X 38. Obstructive atelectasis, aspiration; a child (N.O.).

something to our understanding of the phenomenon. It has shown: (1) that the volume of blood in the lungs increases rapidly following hemorrhage and asphyxia; (2) that the relationship of pulmonary arterial pressure to left atrial pressure is remarkably altered immediately following the release of arterial occlusive tourniquets (see Figures 3 and 4); (3) that stiffening of the lung begins soon after the injection of saline solution, and occasionally

A



B

FIG. 10.—(A) Magnification X 45. Pulmonary infarction, embolism; a man (P.B.). (B) Magnification X 38. Pulmonary edema, cardio-renal failure; a woman (N.P.).

becomes very pronounced in the non-shocked animal while left atrial pressure is falling (this rules out failure of the left ventricle as the universal cause of pulmonary-stiffening); (4) that stiffening of the lung appears soon after the release of arterial occlusive tourniquets and becomes pronounced by the time shock is well established; and (5) that the rapid injection of saline solutions during tourniquet shock, when the lungs have become stiff, quickly causes changes in vascular pressures that are compatible with acute heart failure, and the severity of the shock is increased.

The correlation of clinical experience with experimental experience has served to clarify partially the signs of congestive atelectasis. The very rapid breathing which attends the onset of congestive atelectasis is due evidently to the congestion, and is of reflex origin. Blocking the vagus nerves during congestive tachypnea abolishes it (this observation is not illustrated). The dependence of congestive tachypnea upon pulmonary proprioceptive reflexes was discovered earlier by Churchill and Cope.[7]

The labored breathing seen clinically is most likely a manifestation of the stiffening of the lung. The bronchoscopically visible inward expiratory bulging of the trachea and bronchi associated with congestive atelectasis is likely attendant upon the development of positive intrapleural pressure during expiration, coupled with sufficient congestion of the lung so as to render inward deformation of the larger air passages easier than the deflation of the extrabronchial pulmonary parenchyma.

The resistant cyanosis is manifestly caused by the continuation of a fairly rapid flow of blood through areas rendered airless by the positive increment of blood in the pulmonary capillaries and alveoli.[3] In this respect, congestive atelectasis differs from obstructive atelectasis.[3, 8, 11]

Finally, attention should be called to the almost complete correlation of the clinical pictures of congestive atelectasis and pulmonocardiac failure.[6] The similarity extends even to the common lack of responsiveness to digitalis and to the pulmonary pathologic picture. A kyphotic woman suffering from cardiopulmonary failure whom I had the privilege of observing before and after death showed practically all of the signs of congestive atelectasis before death, and the complete pulmonary picture after death.

SUMMARY

Congestive atelectasis is a complication of the intravenous infusion of fluids. The mortality rate is high.

The clinical picture is characterized by the rather sudden onset of dyspnea, labored expiratory breathing, tachypnea, tachycardia, fever, hypotension that is often aggravated by the transfusion of blood, restriction of thoracic motion, dullness over the involved portions of the lung, the practical absence of roentgen ray signs early, and resistant cyanosis.

Organically, the involved parts of the lung are carnified, but when inflated with air under pressure they inflate and appear grossly normal. Microscopically the process is characterized by capillary congestion, intra-alveolar hemorrhage with little edema, incomplete expansion of alveoli, and compression closure of bronchioles.

The clinical and pathologic pictures and the clinical course of congestive atelectasis is strikingly comparable to pulmonocardiac failure. Even the ineffectiveness of digitalis as a therapeutic agent is common to both syndromes.

Two experimental approaches to the problem have been developed. A preliminary report on some of these studies is made.

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EFFECT OF ANALGESICS AND ANTISPASMODICS ON COMMON DUCT PRESSURES*

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Analgesics and antispasmodics have been the time-honored drugs in the treatment of gallbladder colic and biliary dyskinesia. In view of the many new analgesics and antispasmodics currently offered to the medical profession, it appeared desirable to evaluate their ability in overcoming pain resulting from increased common duct pressure.

Except in unusual circumstances, common duct pressure studies in the normal human being are not feasible. However, an opportunity for these determinations presents itself in instances of cholecystectomies with cholecystostomies. Ivy has shown in dogs that common duct pressure changes following these surgical procedures parallel those in the normal, providing several days are allowed to elapse permitting the surgical inflammatory reaction to subside.

The simplest approach to this study is by connecting a patient's cholecystostomy tube to a water manometer, and recording upon a graph the rise and fall of the manometer's fluid level. The addition of a Y-tube into the system permits one to increase the ductal pressure at desirable periods, thereby determining the necessary pressure required to overcome the sphincter of Oddi tone. Bergh and Ivy employed this technic in their investigation (Fig. 1).

The objection to this method is the absence of a direct and continuous record of the changes in the common duct. In our hands the ordinary manometric floats met too much resistance from the walls of the manometer for accurate recording. At our suggestion, Dr. Warren Gilson† devised an automatic recorder adaptable for studies of this type (Fig. 2). The manometer containing saline solution was connected to the cholecystostomy tube. A weighted copper or platinum electrode suspended over the saline solution in the manometer is connected to an automatic reversing motor by means of a 24K gold-plated chain. When the weighted electrode enters the saline, contact is made and the motor runs in a direction to pull the electrode out of the solution. When the electrode emerges from the saline, contact is broken, the motor reverses itself and the electrode drops. Thus, by this make-and-break contact, with a reversing motor, the electrode dances on top of the saline solution. The movements of the electrode are directly reflected, centimeter for

* Read before the American Surgical Association, Colorado Springs, Colorado, April 19, 1950.

† Doctor Gilson, Assistant Professor of Medical Electronics, University of Wisconsin, will shortly publish the technical aspects of this apparatus.

centimeter, by a pen which inscribes a permanent record on a moving roll of paper.

Our early investigations were not included in this series, since we wished to learn not only the vagaries of the common duct, but also those of our apparatus. The studies were carried out during a fasting period. Unless specifically indicated, drugs were administered intravenously, in order to elicit rapid and demonstrable effects, if any were to be obtained. Whenever possible, several drugs were used on one individual on different days in order to insure proper comparison. When several drugs given to a patient failed to elicit a response in ductal pressure, a check for normal sphincter mechanism was made by employing a drug which consistently reacted well. There were three cases in our series where stones imbedded at the terminal end of the

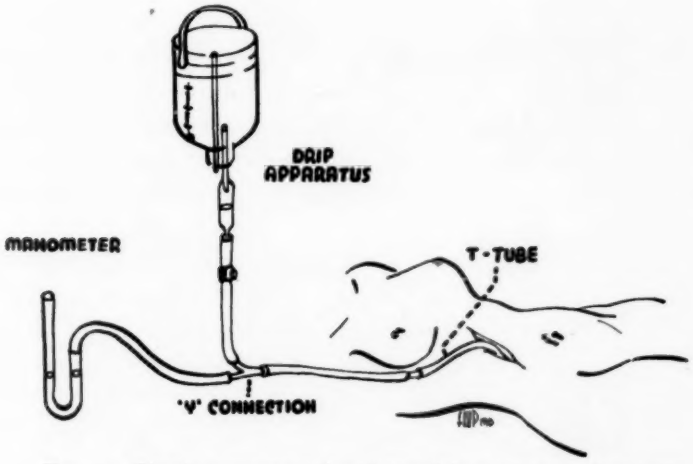


FIG. 1.—Simple apparatus for determining common duct pressures—requires recording of pressure on a graph.

common duct resulted in sphincter scarring or loss of tone, and pressure studies were impossible because the saline solution met little or no resistance.

Twenty-eight patients were studied on 81 occasions, and each time from two to four drugs were investigated. As a rule a spasm-producing agent was followed by one or more antispasmodics. Interestingly, except for Urecholine, all spasm-producing drugs were analgesics. The marked increase in common duct pressures by analgesics provided an excellent opportunity to test the ability of antispasmodics to overcome sphincter of Oddi spasm.

Usually the size of the common duct lumen was readily recognized by the amplitude of the respiratory excursion. With a small lumen the respiratory excursion was narrow, approximating about 2 mm., whereas a large lumen was characterized by excursions up to 1 cm. in width. Physiologic activities, as talking, coughing, laughing, and the Valsalva test, were manifested by a rise

in the common duct pressure. The degree of ductal pressure elevation corresponds to the increase in intra-abdominal pressure (Fig. 3).

The resting common duct pressure was approximately between 4 and 8 cm. of water. An accurate baseline was impossible, since the manometer's level depended on the investigator's impression of the common duct's position. The pressure normally required to overcome the tone of the sphincter of Oddi varied considerably from 10 to 25 cm., with the average being 10 to 15 cm. of water (Fig. 4).

It was possible to elicit pain in practically all patients if saline was introduced rapidly, allowing the common duct to overdistend and the pressure within it to rise quickly. A saline drip of 60 to 100 drops per minute resulted

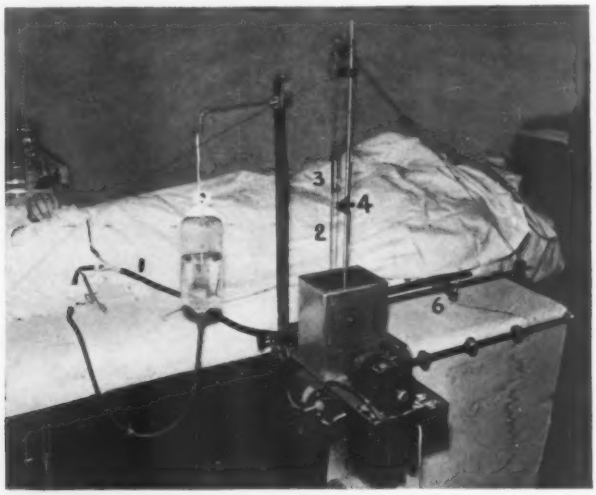


FIG. 2.—Gilson Mechanical Recording Machine: (1) Cholecystostomy tube to manometer; (2) manometer containing saline solution; (3) weighted electrode; (4) 24 k. gold plated chain; (5) reversing motor unit, and (6) pen inscribing on roll of paper.

in a gradual rise in pressure. Under this circumstance, pain developed when the sphincter tone permitted a ductal pressure elevation of 20 or more centimeters. In a few instances pain was noted at levels between 15 and 20 cm. of water.

Table I demonstrates that if its tone is intact, clinically prescribed doses of analgesics will produce a high degree of sphincteric spasm. Morphine, particularly, was associated with an unusual degree of spasm. Codeine gr. 1, and Dolophine 5 mg., produced somewhat less spasm than the other analgesics. Two of our earlier cases receiving Demerol failed to raise the common duct pressure. After observing this drug in later cases, its consistent rise in pressure led us to suspect strongly that its earlier failure could well have been due

FIG. 3

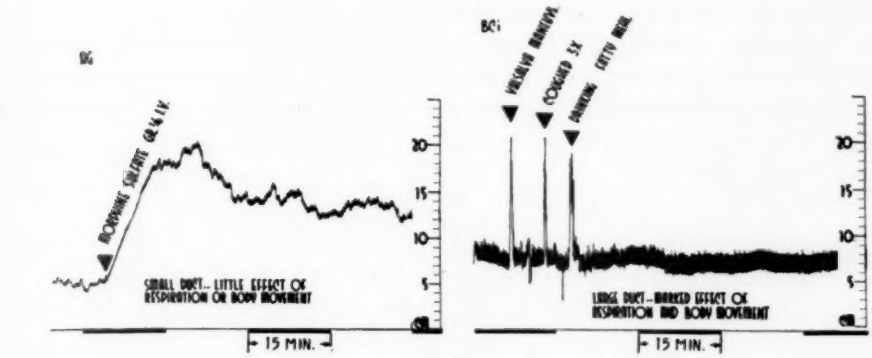
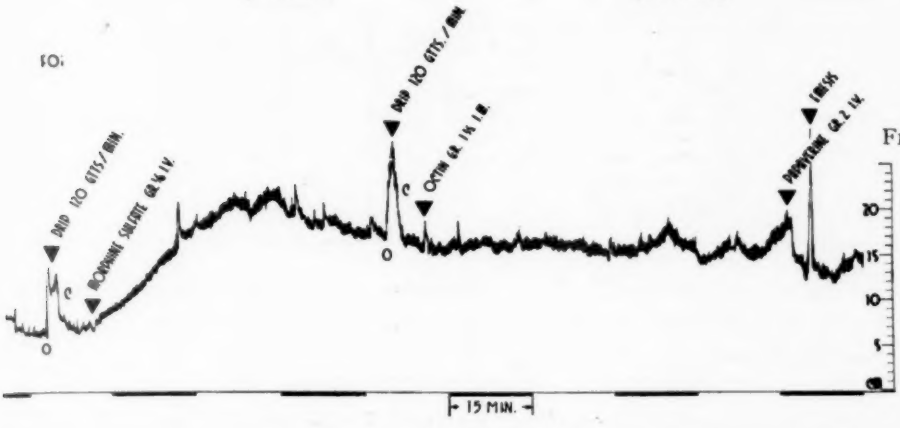


FIG. 4



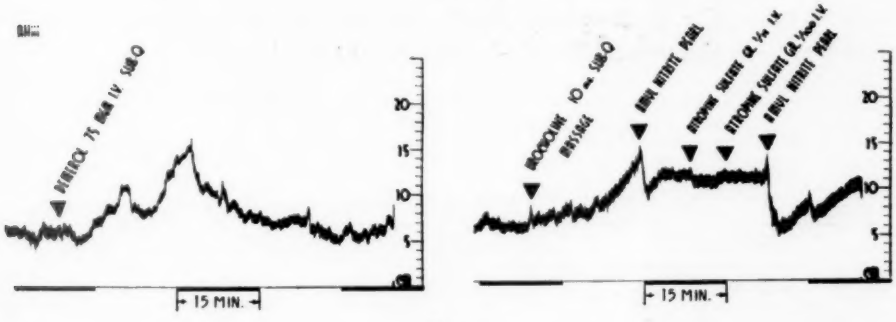


FIG. 5

FIG. 3.—Left—This demonstrates narrow respiratory excursions associated with small common bile duct. Right—This demonstrates wide respiratory excursions with large common bile duct. Also, it shows increased ductal pressures with coughing, drinking, and the Valsalva test.

FIG. 4.—Normal resting pressure—6 cm. of H_2O. Normal resistance of the sphincter of Oddi—15 cm. of H_2O, common duct pressure rise following morphine—20 cm. of H_2O, pressure required to overcome sphincteric spasm—33 cm. of H_2O.

FIG. 5.—Demerol and Urecholine given subcutaneously—rise in ductal pressure is definite although gradual.

to a scarred and nonfunctioning sphincter. Unfortunately these two patients were not checked with a morphine response.

Urecholine was suggested because, as a parasympathetic stimulator, it should increase smooth muscle tone, but at the same time relax the sphincters. Accordingly, Urecholine was given after spasm was induced with dilaudid. Imagine our amazement when, instead of reducing the ductal pressure, the

TABLE I.—*Spasm Producing.*

Drug	Dose	No. of Administrations	Degree of Spasm			
			None	Min.	Mod.	Marked
Morphine	Gr. 1/6	39	0	0	4	35
	Gr. 1/8	3	0	1	2	0
Pantopon	Gr. 1/3	2	0	0	0	2
Dilaudid	Gr. 1/48–1/32	4	0	0	1	3
Dromoran (Nu-2206)	Mg. 5	5	0	1	0	4
Demerol	Mg. 75–100	7	2	0	1	4
Codeine	Gr. 1	3	0	0	3	0
Dolophine	Mg. 5–10	7	1	1	4	1
Urecholine, subcutaneous (Combined with Dilaudid)	Mg. 5	2	0	0	0	2
Urecholine, subcutaneous (Alone)	Mg. 5	3	0	1	2	0

two drugs acted synergistically, the pressure rising to great heights, resulting in colic and vomiting. When given alone the Urecholine produced but a moderate rise in common duct pressure.

The question was raised that the intravenous use of these drugs did not necessarily reflect the subcutaneous response. Demerol and Urecholine given in this manner (Fig. 5) definitely elevated the common duct pressure. The rise, however, was slower and the elevation less sustained.

TABLE II.—*Antispasmodics.*

Drug	Dose	No. of Administrations	Degree of Relaxation			
			None	Min.	Mod.	Marked
Amyl nitrite	Pearl	16	0	0	2	14
Amyl nitrite (after other drugs failed)	Pearl	8	0	0	1	7
Aminophyllin	Grs. 7½	3	0	1	2	0

The vast majority of antispasmodics, when administered in the usually prescribed doses, failed to overcome the spasm produced by analgesics. Amyl nitrite and aminophyllin were the only two drugs which appeared to decrease the pressure.

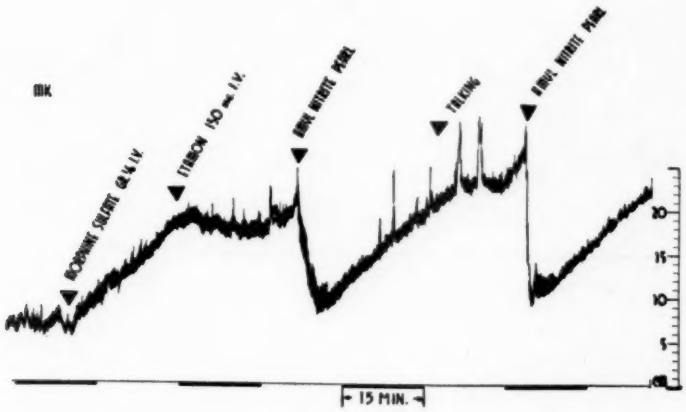
Amyl nitrite characteristically produced a precipitous, but unfortunately temporary, drop in the common duct pressure lasting from three to five minutes, then rising to the previous level of spasm (Fig. 6). The ability of amyl nitrite to control a biliary dyskinesia was shown in a patient (Fig. 7) developing right upper quadrant pain and nausea. The common duct pressure was

elevated, and following inhalation of amyl nitrite, the ductal pressure dropped to normal and her symptoms were completely relieved.

Aminophyllin produced a minimal to moderate drop in pressures (Fig. 8).

Atropine 1/100 gr., nitroglycerin 1/100 gr., and papaverine ½ to 1 gr., had little or no effect in reducing the common duct pressure.

FIG. 6



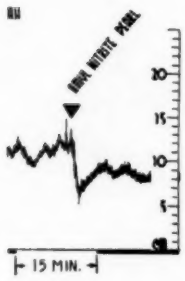


FIG. 6.—Effect of amyl nitrite on sphincteric spasm.

FIG. 7.—Effect of amyl nitrite on biliary dyskinesia.

FIG. 7

TABLE III.—*Antispasmodics.*

Drug	Dose	No. of Administration	Degree of Relaxation			
			None	Min.	Mod.	Marked
Nitroglycerin	Gr. 1/100	7	6	1	0	0
Papaverine	Gr. ½-1	4	4	0	0	0
Atropine (response to analgesic spasm)	Gr. 1/75-1/100	3	2	1	0	0

Recently it was decided to double the dose of the above antispasmodics (Table IV). Admittedly the number of cases studied is insufficient for a final evaluation. Nevertheless the results were encouraging. Nitroglycerin gr. 1/50, produced moderate to excellent drop in pressure. Papaverine gr. 2, acted similarly, although occasionally it induced vomiting (Fig. 9). Atropine was most disappointing, for even with doses as high as 1/33 of a grain there was no

FIG. 8

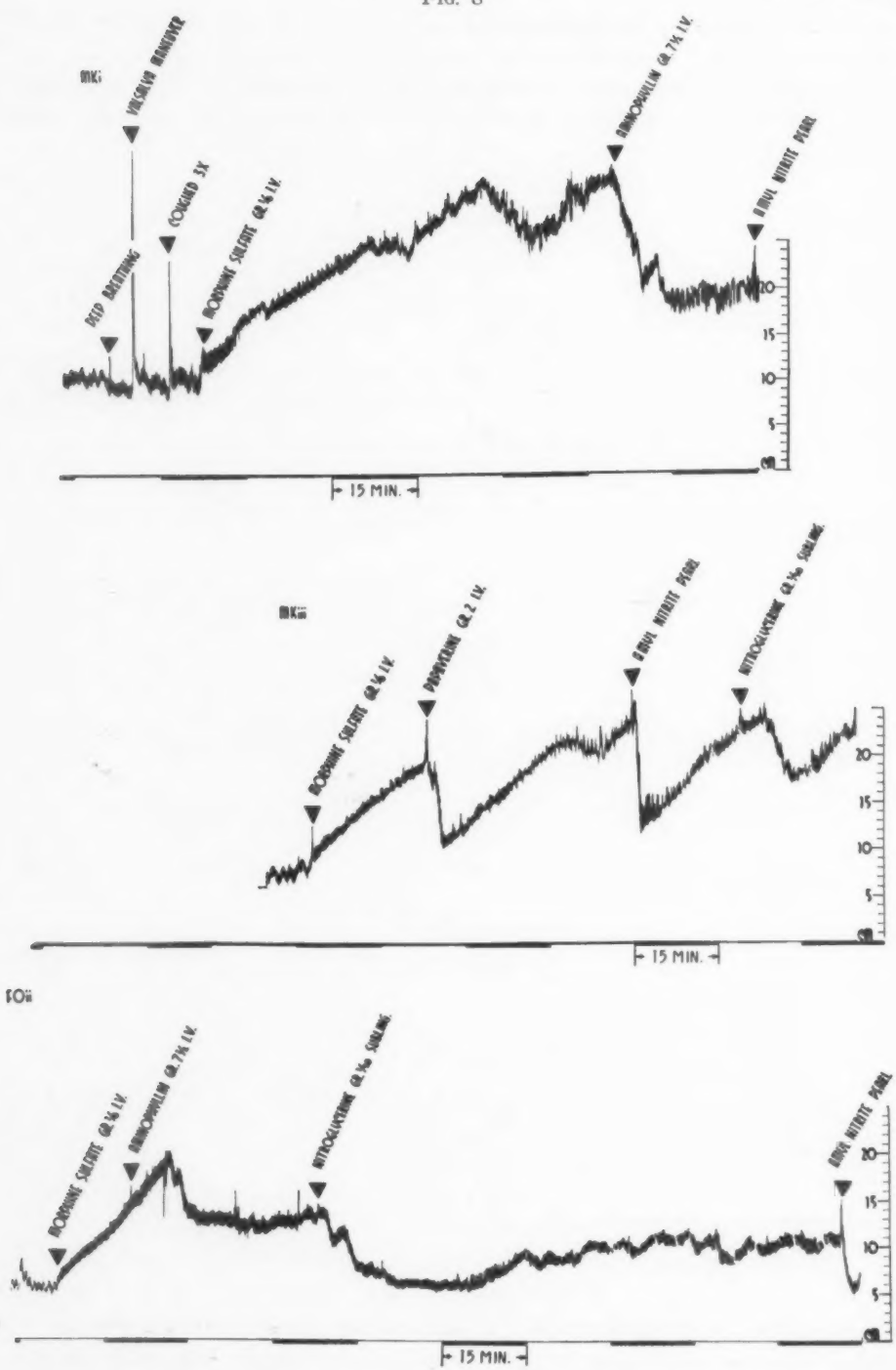


FIG. 9

FIG. 8.—Moderate, more sustained, drop in common duct pressure by aminophyllin.

FIG. 9.—Effect of large doses of papaverine and nitroglycerin in overcoming common duct spasm.

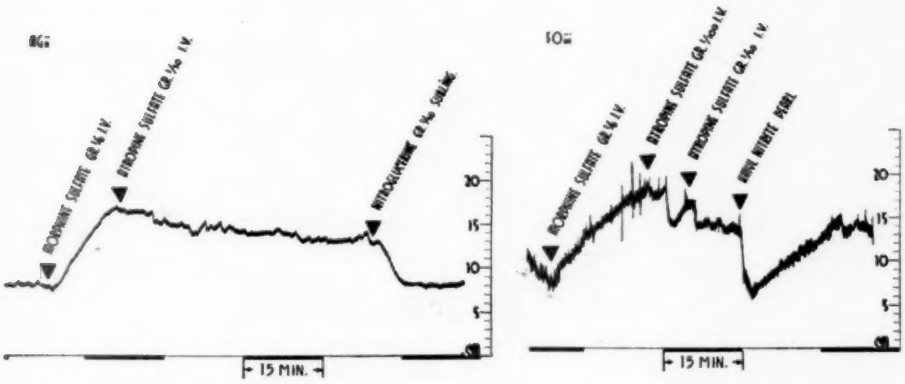
appreciable change in the common duct pressure (Fig. 10). Atropine proved no more efficacious when given prior to administration of Dolophine (Fig. 11).

The popular synthetic antispasmodics were given a trial (Table V). Syntropan 75 mg., Pavatrine 75 mg., Amethone 75 mg., Nu-2172 5 mg., and

TABLE IV.—*Antispasmodics.*

Drug	Dose	No. of Administrations	Degree of Relaxation			
			None	Min.	Mod.	Marked
Nitroglycerin	Gr. 1/50	3	0	0	1	2
Papaverine	Gr. 2	3	0	1	1	1
Atropine (response to analgesic spasm)	Gr. 1/50–1/33	3	2	1	0	0
Atropine (response to Urecholine spasm)	Gr. 1/50	1	0	1	0	0

FIG. 10



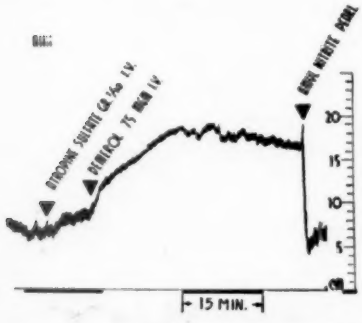


FIG. 11

FIG. 10.—Large doses of atropine do not alter sphincter spasm.

FIG. 11.—Atropine given prior to Demerol.

Octin gr. 1½, all failed to lower the common duct pressure to any extent. A typical response from these drugs is seen in Figure 12. Since they have a belladonna-like action, a response similar to that of atropine would be anticipated. Therefore, on the basis of atropine results it appears improbable that

increasing the dose will improve the effectiveness of these drugs. Nonetheless a few screening trials with larger doses will be tried.

Table VI indicates that fatty meal, Nitranitol, Etamon and splanchnic

FIG. 12

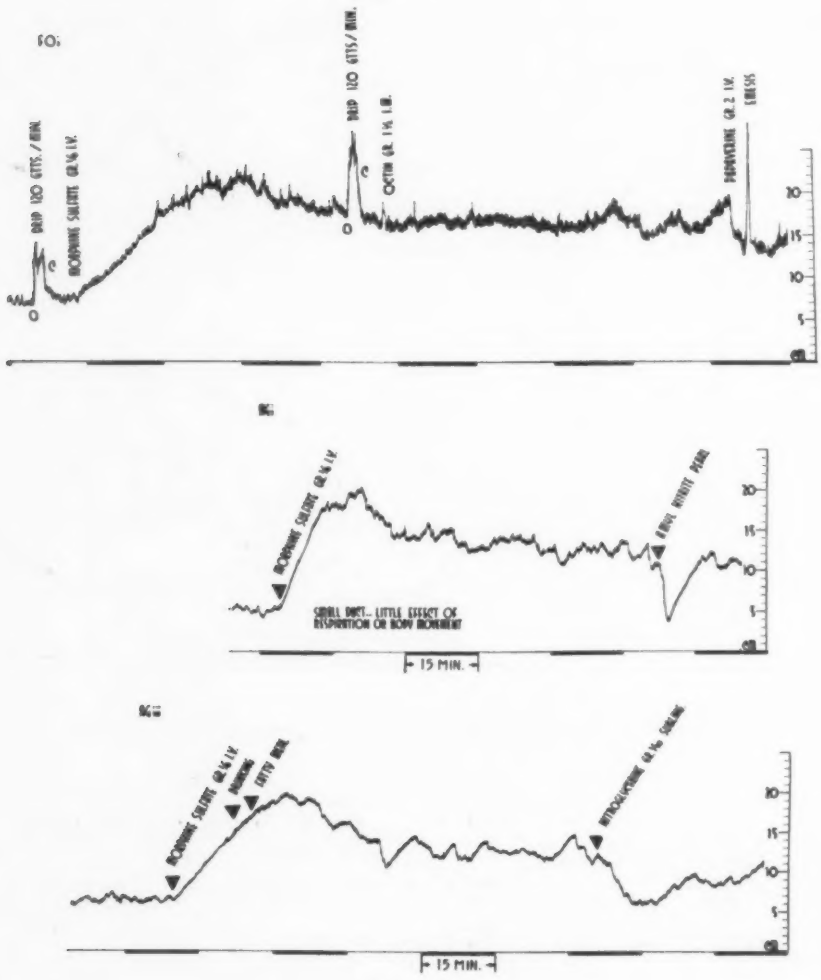


FIG. 13

FIG. 13.—Top—Response of common duct to morphine stimulation. Bottom—Inability of fatty meal to alter pressure changes produced by morphine.

blocks were unable to reduce common duct pressures, while DHO 180 might prove of value. The number of cases, however, is too few for a positive statement.

It is generally assumed that fatty meals relax the sphincter and stimulate gallbladder contraction. We are in agreement with Doubilet and Colp, for, from our studies, fatty meals, when given either before or after morphine stimulation, failed to show any lowering of the common duct pressure (Fig. 13).

Inasmuch as amyl nitrite was such an effective temporary spasmolytic, it was considered advisable to try Nitranitol in the hope it would have a prolonged effect. Nitranitol, gr. 1, was given every three to four hours to a patient for 24 hours prior to his test. Despite this saturation with the drug 10 mg. of Dolophine resulted in a good rise in pressure, although it probably was not as well sustained as in the control group (Fig. 14).

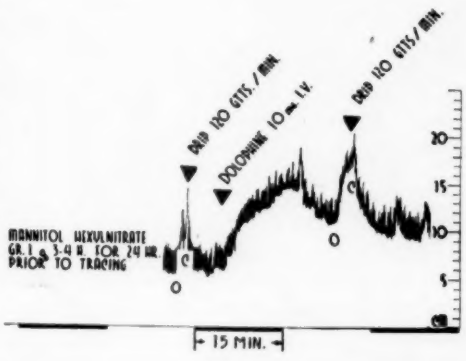


FIG. 14

TABLE V.—*Antispasmodics.*

Drug	Dose	No. of Administrations	Degree of Relaxation			
			None	Min.	Mod.	Marked
Syntropan	Mg. 75	9	6	2	1	0
Pavatrine	Mg. 75	3	2	1	0	0
Amethone	Mg. 75	1	1	0	0	0
Nu-2172 (Hoffmann-LaRoche)	Mg. 5	5	5	0	0	0
Octin, intramuscularly	Gr. 1¼	2	2	0	0	0

TABLE VI.—*Antispasmodics.*

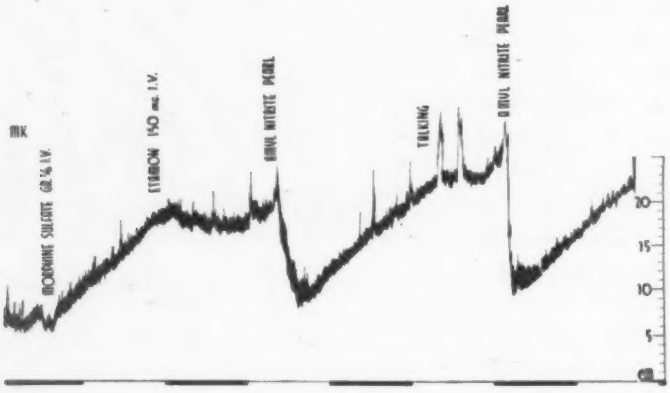
Drug	Dose	No. of Administrations	Degree of Relaxation			
			None	Min.	Mod.	Marked
Fatty meal		2	2	0	0	0
Nitranitol	Grs. 1 q. 3 hrs.	2	2	0	0	0
Etamon	Mg. 150	2	2	0	0	0
DHO 180	Grs. 1½–2	3	1	1	1	0
Splanchnic block	Bilateral	1	1	0	0	0

Etamon 150 mg., a drug preventing transmission of autonomic stimuli by blocking the ganglia, failed to lower the ductal pressure (Fig. 15). DHO 180 gr. 1½ to 2, which blocks the sympathetic system, showed promise by reducing the common duct pressures minimally to moderately (Fig. 16).

The role of the autonomic nervous system in controlling the sphincter of Oddi can best be gauged either by a bilateral splanchnic block or by denervation of the common duct. Denervation of the duct proximal to its retro-

duodenal portion is possible. This procedure would obviate pain sensations arising either from the gallbladder or from neuromas in this area, but it would not control the nerve supply to the sphincter which, we believe, most likely follows the path of the gastroduodenal artery. At any rate, a denervation of

FIG. 15



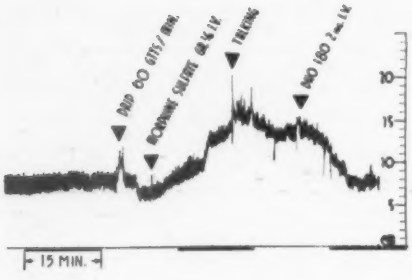


FIG. 16

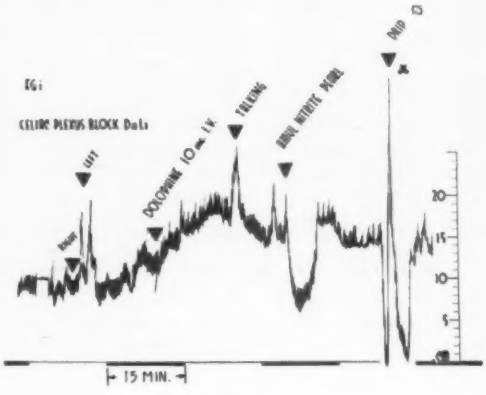


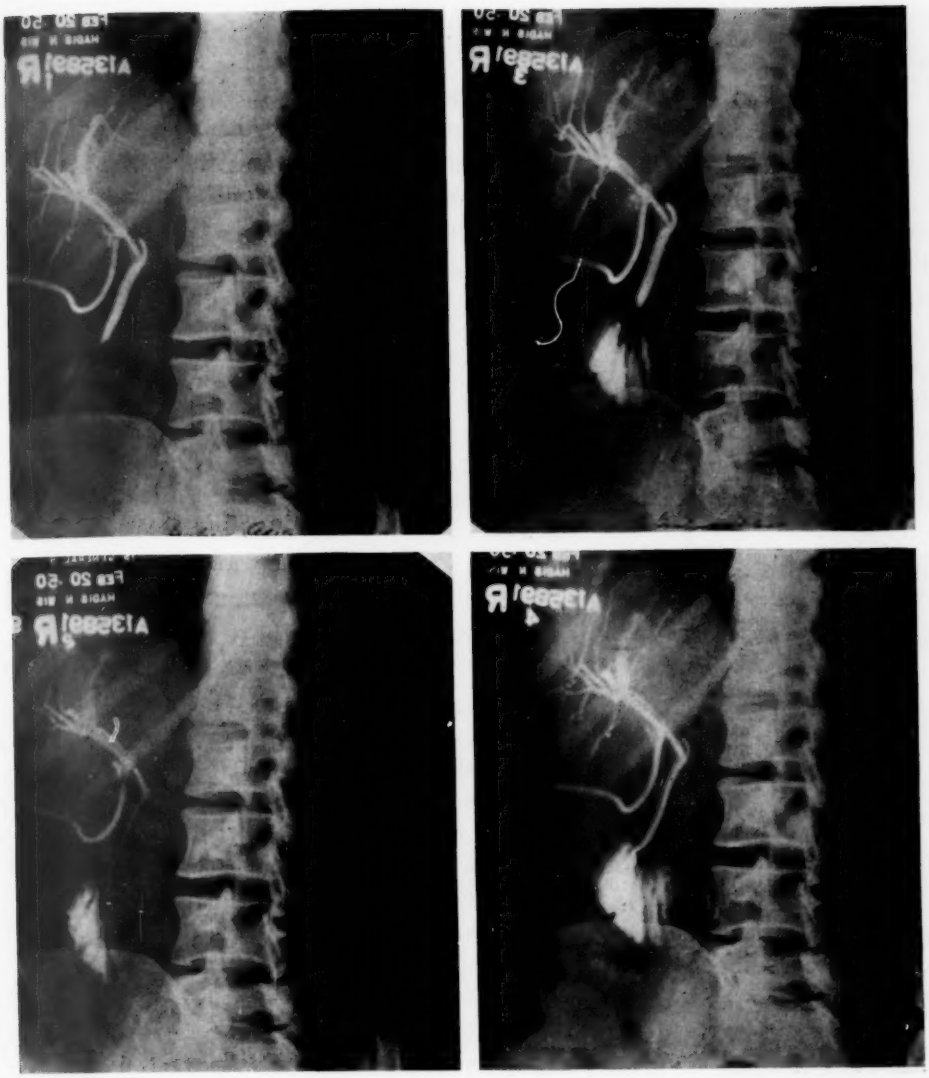
FIG. 17

FIG. 16.—Effect of DHO 180 on common duct spasm.

FIG. 17.—Bilateral splanchnic block does not prevent rise in common duct pressure. There was no pain at point x when pressure was raised to 40 cm. of H_2O.

the common duct in the lesser omentum in one case failed to inhibit sphincteric spasm.

In another patient a bilateral splanchnic block also did not prevent a rise in common duct pressure when Dolophine was given intravenously. This study demonstrated an interesting sidelight. One hour following the splanchnic block the ductal pressure was raised to 40 cm. of water, and except for slight fullness the patient experienced no ill effect. The following day elevation of ductal pressure to 18 cm. created severe pain (Fig. 17).



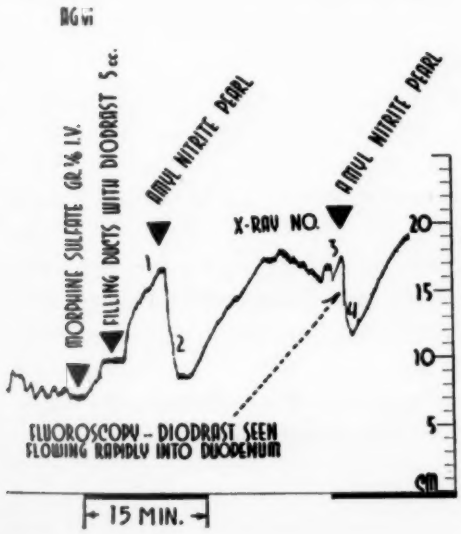


FIG. 18.—Pressure studies combined with radiologic visualization. Upper left roentgen ray was taken at point 1. Left lower roentgen ray was taken at point 2. Upper right roentgen ray was taken at point 3. Right lower roentgen ray was taken at point 4.

It has been postulated that the drop in common duct pressure may be due to a relaxation and distention of the biliary system rather than a spasm of the sphincter of Oddi. On two occasions pressure recordings were combined with radiologic studies which, in our opinion, rather conclusively demonstrated that ductal pressure elevations were caused by a spasm of the sphincter of Oddi. Figure 18 represents one of these studies. Here morphine gr. 1/6, was given intravenously and a few minutes later 5 cc. of fluid was withdrawn from the biliary system and replaced with 5 cc. of Diodrast. At point 1 a roentgenogram was taken showing the Diodrast filling only the biliary tree. Immediately after the film was taken a pearl of amyl nitrite was inhaled, and 60 seconds later a second roentgenogram showed the dye entering the duodenum. The test was repeated after the common duct pressures had returned to their elevated levels and the opaque dye was out of the system. Diodrast was again introduced into the biliary system. Roentgen ray films at this point showed it limited to the biliary tree. Shortly after, amyl nitrite was inhaled at point 3. Within 15 seconds, through fluoroscopy, it was possible to see the Diodrast rapidly flowing into the duodenum at point 4.

CONCLUSIONS

1. Physiologic activities, such as talking, walking, coughing and straining increased the common duct pressure.

2. The pressure ordinarily required to overcome the sphincter of Oddi tone causes neither pain nor discomfort.

3. However, analgesics, parasympathetic stimulators as Urecholine, and other agents may increase the sphincter tone to a point where ductal pressures will rise to a pain producing level (biliary dyskinesia). This level is 20 or more centimeters of water pressure.

4. Analgesics as a group are powerful stimulators of the sphincter of Oddi when given in the usually prescribed doses. The resulting rise in ductal pressures may accentuate, rather than lessen, biliary colic. Therefore, the effective pain relieving dose for biliary colic must be sufficient to produce marked central nervous system depression.

5. Except for amyl nitrite and possibly aminophyllin, antispasmodics given in clinical doses were extremely disappointing and failed to overcome the analgesic produced spasm.

6. Amyl nitrite definitely and consistently responded by lowering ductal pressures for short periods.

7. When nitroglycerin and papaverine were given in large doses of 1/50 gr. and 2 gr. respectively, an effective lowering of ductal pressure was noted.

8. Atropine in doses up to 1/33 of a grain failed appreciably to alter the ductal pressures.

9. The synthetic antispasmodics Syntropan, Pavatrine, Amethone, Nu-2172 and Octin apparently have no effect on the sphincter of Oddi.

10. Fatty meals, Nitranitol, and Etamon also failed to lower ductal pressure.

11. DHO 180 and splanchnic block warrant further study.

12. Apparently splanchnic block does control pain due to overdistention and increase in common duct pressure.

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DISCUSSION.—DR. JEROME P. WEBSTER: I do not wish to talk on plastic surgery of the common duct. I would like to say for the record, however, that in 1920 when Dr. Mont Reid was using his cysticocholedochostomy, after having taken out the gall bladder, explored the common duct, removed the stones and sutured his common duct, he dilated the cystic duct and inserted a tube through the cystic duct into the common duct. He tied this in place. I was working with him then, and at that time, instead of having a single drainage tube go down to a bottle, I put in a Y-tube and made observations with the manometer, and also with a long glass tube which went horizontally at the level of the common duct.

The observations were very crude and simple at that time, but they did show to us that in particular we had a record of the intraperitoneal pressure. It was difficult to try to explain the difference between the intraductal pressure and the intraperitoneal pressure.

The elevation caused by coughing, raising of the leg and, of course, the respiratory pressure, were noted at that time.

This was followed by experiments on dogs, which were not conclusive, and which were terminated when I left for China. Undoubtedly, experiments on the human being would be far more satisfactory than on dogs.

Dr. Reid reported those observations in the ANNALS OF SURGERY shortly afterward. I do not know if those were the first such observations made. You will probably find that many other earlier observations were made, but I thought you would be interested in it from a historical standpoint.

DR. A. R. CURRERI (in closing): I would like to thank Dr. Webster for his remarks. We, too, observed similar changes in common duct pressures which parallel the pressure changes in the peritoneal cavity. Because of this, it was imperative throughout these studies to maintain patients at absolute rest. In this preliminary report, credit is given to only a few of those who have investigated this problem. Due credit will be given in a later communication.

FURTHER STUDIES ON FACTORS INFLUENCING LIVER INJURY AND LIVER REPAIR*

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The morbidity and mortality of surgical lesions involving the biliary tract have decreased progressively during the past quarter of a century. This desirable circumstance is in large part due to the results obtained from animal experiments, which have been applied to similar conditions occurring in man. In few fields has the application of the results of animal experimentation been more fruitful in extending existing knowledge of the patho-physiology of diseased processes than in the liver.

In spite of these advances in our knowledge of hepatic injury much remains unknown. There are not now available methods for accurately detecting even moderate degrees of chronic liver injury. It is often surprising how extensive the histologic change may be, and yet the currently available function tests provide little information that a superimposed acute injury may well induce hepatic incompetency. In few parenchymal organ systems is histologic appearance in chronic disease apt to be so poorly reflected by function tests.

On the other hand, acute hepatic cellular injury, from any cause, is most frequently associated with striking changes in function as determined by these tests, even when histologic evidences of parenchymal injury may be minimal. It is for reasons such as these that widespread biliary cirrhosis resulting from repeated attacks of cholangio-hepatitis may be associated in the chronic state, with little or no evidence of functional incapacity as determined by the turbidity and flocculation tests; and major evidences of functional abnormality may be found in patients with relatively mild attacks of viral hepatitis, in which the histologic evidence of cellular injury is minimal.

We know of no other organ in the body that possesses such an irresistible urge to regenerate after injury even under unfavorable conditions; but it should be just as readily recognized that few organs are more susceptible to a wide variety of noxious agents. Perhaps a wider understanding of certain factors recently shown to cause and to implement widespread hepatic parenchymal injury and the therapy now available which will facilitate repair, will result in a further reduction in the morbidity and mortality of patients with biliary tract disease subjected to operation.

* The research upon which this paper is based was done in part under a contract with the Department of the Army and the University of Pennsylvania. Read before the American Surgical Association, Colorado Springs, Colorado, April 19, 1950.

ANOXIA AND LIVER INJURY

There are essentially two mechanisms by which anesthesia can effect the hepatic parenchyma—one by direct toxic action of the anesthetic agent and the other by the imposition of anoxia on the parenchymal cells. Every anesthetic agent is not toxic or necrotizing to hepatic cells, although many are. No anesthetization, general or spinal, is without effect on these cells if, during anesthesia and operation, from whatever cause, there occur periods, long or short, where the hepatic cells suffer from oxygen want (Fig. 1).

In the liver which is essentially normal histologically, short periods of oxygen starvation may produce no demonstrable histologic or functional

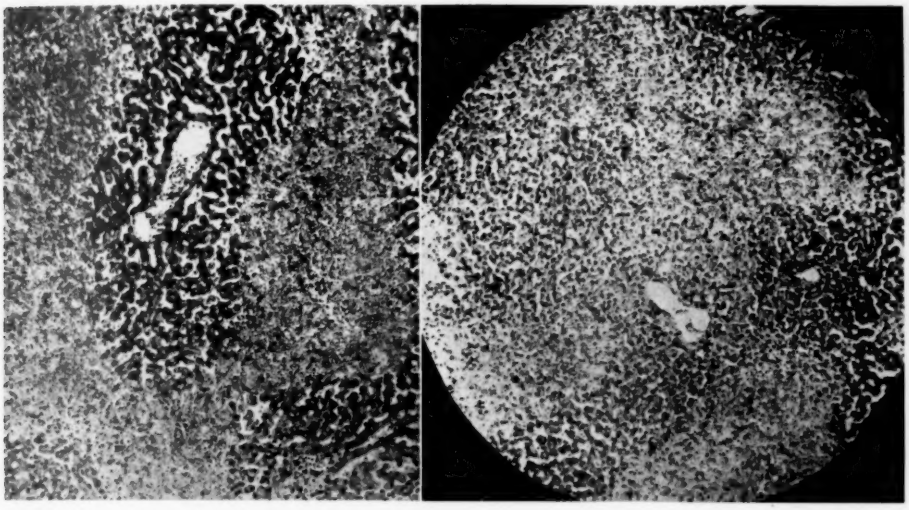


FIG. 1 FIG. 2

FIG. 1.—Necrosis of the liver following ether anesthesia.
FIG. 2.—Necrosis of the liver following nitrous oxide and oxygen anesthesia.

change; but where serious cellular injury, acute or chronic, already exists, even short periods of anoxia may be the motivating factor leading to hepatic incompetency. It must be constantly kept in mind that the hepatic parenchyma is exceedingly susceptible to oxygen want from any cause.

Chloroform volatilized with air for anesthesia in the experimental animal is twice as necrotizing as when the chloroform is volatilized with oxygen. Even nitrous oxide and oxygen, when insufficient oxygen is used in the mixture, can cause so extensive a necrosis of the liver that the resultant histologic picture may be indistinguishable from that produced by chloroform (Fig. 2).

Any circumstance that unfavorably influences blood flow, or is associated with a decreased oxygen saturation of the arterial blood, will result in injury to the liver cells. Such a condition may initiate injury or may accentuate existing damage.

The evidence now available from many laboratories strengthens the importance of an adequate and optimal oxygen supply to the liver cells during and after operation.

The work of Shorr[1] and Fine[2] and their associates points strongly to the liver as the organ conditioning the development of irreversible shock, while more recent experiments have demonstrated the amazing protection which well oxygenated blood introduced into the portal circulation provides in preventing the development of this serious state.[2a]

There are other factors which may cause local anoxia even when the peripheral evidences of oxygen want may be lacking. The placing of retractors along the right free border of the gastro-hepatic omentum so as to interfere with the normal blood flow to the liver may result in acute hepatic cellular degeneration and necrosis.

Estrada, Simpson and Vars[3] have demonstrated that massive or confluent centrilobular necrosis will occur in the rat following massive gastric distention, and that this is even more marked in the period immediately following partial hepatectomy. The importance of minimizing gastric and intestinal distention in patients with extensive liver injury has received little attention in surgical literature, and yet such a circumstance may so impede hepatic blood flow as to precipitate cellular changes leading to functional incompetency.

To prevent an occasional catastrophe, it may be necessary to maintain gastric intubation for several days after operation in all patients known to have, or suspected of having, pre-existing hepatic parenchymal injury.

Drugs which adversely affect the respiratory exchange, such as morphine and the barbiturates, have long been known to be poorly tolerated by patients with liver injury. Every clinician of experience has observed patients with serious liver injury making a relatively satisfactory recovery from the initial effects of anesthesia and operation, and then, following the injudicious use of such drugs, show evidences of hepatic failure. The anesthetist must be warned of this circumstance, and young house officers must constantly be cautioned that respiratory depressants are to be used in patients with widespread hepatic injury only when all other measures to relieve pain have proved ineffectual. It is well to remember that such a time-honored sedative as chloral hydrate has never been shown to cause hepatic injury.

THE EFFECT OF PROTEIN STARVATION IN CONDITIONING LIVER INJURY

It is now generally agreed that a diet adequate in composition and in total calories facilitates repair of an injured liver. It is not so generally accepted that under-nutrition frequently conditions the extent of the hepatic injury which results following exposure to an hepatotoxic agent.

Goldschmidt, Vars and Ravdin[4] demonstrated that the most important dietary component in conditioning the liver against injury by noxious anesthetics was protein. They demonstrated that in general the higher the lipid

concentration of the liver, prior to anesthetization with such agents, the greater was the cellular injury; but that an adequate amount of protein in the diet for several days prior to anesthetization provided some protection to the liver even in the presence of large increments of hepatic lipid.

It has now been demonstrated by other investigators[5-7] that dietary protein will protect the liver from a wide variety of noxious drugs and that protein starvation, or under-nutrition, increases the susceptibility of the liver to these agents. It is not so generally recognized that just as protein starvation accentuates the hepatic necrosis produced by certain drugs, so, too, protein starvation accentuates the injury produced by anoxia. Estrada, Simpson and Vars[3] found more widespread hepatic necrosis in the protein-starved animals following gastric distention than in well-fed animals. The demonstration by

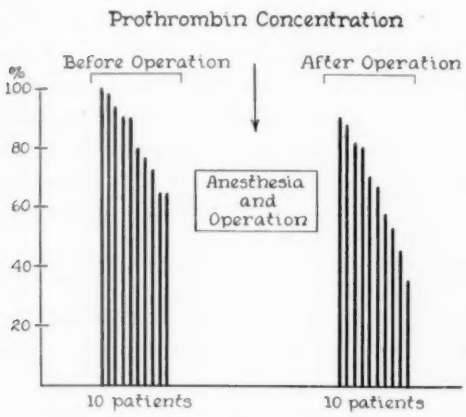


FIG. 3

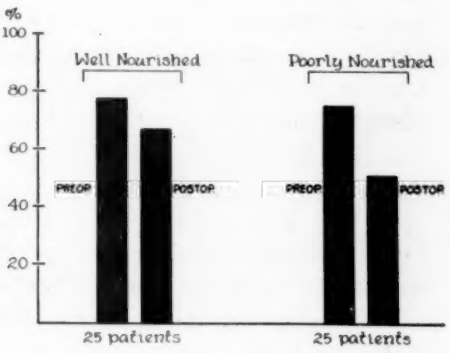


FIG. 4

FIG. 3.—Prothrombin concentration before and after anesthesia.
FIG. 4.—Change in prothrombin concentration at two nutritional levels.

these workers that the more protein-depleted the liver was prior to exposure to gastric distention the more extensive was the resultant injury illustrates the importance of a carefully carried out dietary program prior to operation.

The beneficial effect of protein repletion prior to operation can be demonstrated in man by comparing prothrombin determinations before and after operation in patients with hepatic disease (Fig. 3). An adequate concentration of prothrombin prior to operation may become sharply reduced subsequent to operation by any one or combination of factors which cause parenchymal injury. We have observed, in patients whose dietary intake for some time prior to anesthesia has been adequate, that this sharp decline is minimized in comparison to those whose intake has been inadequate.

It is frequently impossible to determine the protein competency of these patients by any laboratory tests for total proteins, and fractionated proteins may at times give no direct clue to the actual protein intake in the presence

of serious parenchymal change. A careful history prior to hospitalization and an accurate dietary record subsequent to hospitalization are often more revealing than are the laboratory determinations.

Using these criteria, in addition to laboratory tests, to provide the classification of the degree of nutritional repletion or deprivation, we have found the mean fall in the prothrombin concentration on the second postoperative day to have been 10.3 per cent in the well fed group, while in the patients whose mean prothrombin concentrations prior to operation were nearly identical and who had been on a poor dietary intake, the mean decline in concentration on the second postoperative day was 26.2 per cent (Fig. 4).

The evidence now available points strongly to nutritional factors as important etiologic agents in the production of liver injury, either in the form of degeneration or necrosis in acute injury, or as cirrhosis in chronic injury. When the effect of the injurious agent is overwhelming, as occurs in anoxia, the exposure to hepatotoxins and certain bacterial and viral infections, necrosis results. It will also be observed when previous injury provides hepatic parenchyma whose resistance to additional injury has been lowered. On the other hand, repeated exposure to the same injurious agent in lesser amounts will frequently result in some degeneration, associated with a variable degree of cirrhosis.

INFECTION

We have previously called attention to the fact that the problems associated with acute cholangio-hepatitis are not so serious as they were prior to the availability of the more recently discovered antibiotics. Aureomycin, with its wide antibacterial spectrum, has been used by us with gratifying results. The use of such agents exerts no effect on the underlying cause of the cholangio-hepatitis, but control of the active infection permits operation for the removal of common duct obstruction due to stone or stricture under much more favorable circumstances.

The striking results obtained by Markowitz, Rappaport and Scott[8] following ligation of the hepatic artery of the dog when these animals were protected with penicillin, and the substantiation of these observations by Fitts and Scott[9] and their subsequent observations of the even greater effectiveness of aureomycin in protecting such animals from an otherwise inevitable death, emphasizes again the usefulness of antibiotic therapy.

COINCIDENTAL LIVER AND RENAL INJURY

There has long been serious question as to whether the "hepato-renal syndrome" actually exists. It has now been shown that under certain experimental conditions definite histologic changes may be found in the liver and kidneys of animals exposed to certain noxious agents or to a special dietary program. Either a choline deficient diet or cirrhosis-producing diet will frequently cause simultaneous liver and renal injury, the latter exhibiting itself

chiefly by acute cortical injury. The dietary factors which lead to recovery from the hepatic cell injury will have a beneficial effect on the renal lesions.

ENZYME ACTIVITY IN THE REGENERATING LIVER

Rosenthal, Vars, Rogers and Fahl[10] have, in view of the biological significance of premitotic cytochemical, studied the enzyme activity of the regenerating rat liver from a half day to eight days after 70 per cent partial hepatectomy. The influence of preoperative protein-depletion and postoperative fasting was also investigated. The following enzymes were assayed: arginase, alkaline phosphatase, adenosine-pyrophosphatase, rhodanase, cholinesterase, and common esterase. With the latter four enzymes, activity per gram of liver protein started to decline just before onset of increased mitotic activity. During the subsequent phase of highest rate of cell multiplication and protein synthesis, activity of these enzymes was reduced by about 20 per cent, and then gradually returned to the original level. The inverse order of changes was found with arginase and alkaline phosphatase, the maximal activity being reached at the onset of increased mitotic activity. The magnitude of the increase of enzyme activity was related to extent and direction of the postoperative change in the animal's metabolism. It thus is evident that during the initial phase of normal regenerative growth pronounced changes in the enzyme pattern are taking place which subsequently disappear in the course of cell division and maturation. It seems possible from their work that stimuli to cell multiplication are transmitted through distortion of enzyme patterns in response to changing environmental conditions.

DIET AND LIVER REPAIR

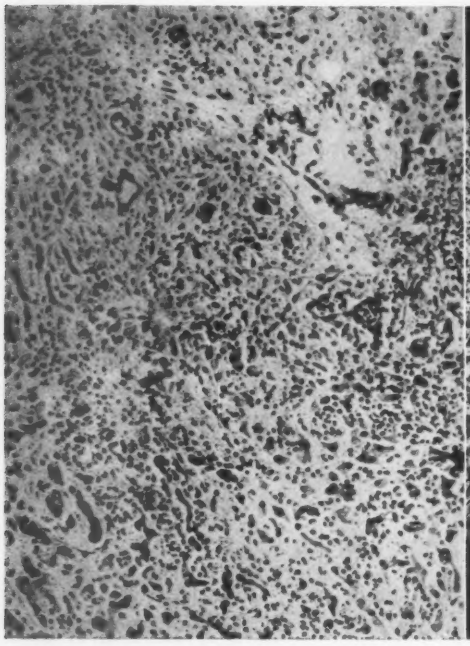
Goldschmidt, Vars and Ravdin[4] concluded from their studies that a diet rich in carbohydrate and protein and low in fat was the diet best calculated to prepare the patient with liver injury for anesthesia and operation, and to facilitate repair thereafter.

During the course of these early experiments data were obtained which demonstrated that if the diet contained a sufficient amount of a high quality protein, the dietary fat could be considerable without increasing the liver lipid during the period of special feeding. In such circumstances, the liver lipid decreased quite as rapidly as if the fat were restricted in the diet. In 1945, Hoagland[11] suggested that if the fat in the diet of patients with infectious hepatitis were not restricted to the degree we had suggested, the total caloric intake, which is as important as the composition of the diet, would be greatly increased.

Vars and Gurd[12] have further clarified the relationship of diet to repair in the regenerating liver. They have shown that following partial hepatectomy in the rat, regeneration during a period of two weeks is dependent upon the quality and the amount of protein fed in an otherwise calorically sufficient dietary. Zein as a source of protein was no better than no protein in the diet,

while 27 per cent of casein was considerably better than 18 per cent of casein. The ability of the liver to utilize protein from endogenous or exogenous sources, for rapid repair, was the most important factor in the survival of the animals subjected to preoperation protein depletion and partial hapetectomy.

Vars, Friedgood, Ferguson and Rogers[13] have now studied regeneration of the liver during periods of a high fat dietary. They have studied the effect of high carbohydrate, high protein, low fat and high fat dietaries on regeneration of the liver of the rat following partial hepatectomy. They have



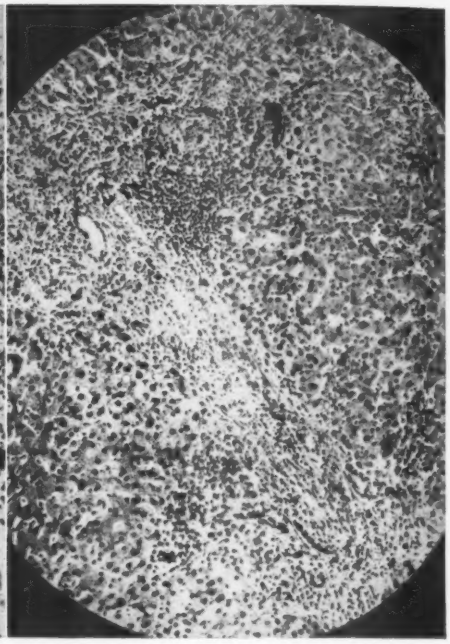


FIG. 5 FIG. 6

FIG. 5.—Widespread cholangiohepatitis with necrosis. Even though the necrosis is extensive mitotic cells are present.

FIG. 6.—Regeneration of hepatic cells in cholangiohepatitis. Twenty days between biopsies.

found that as much as 30 per cent of the total calories can be ingested as fat without unfavorably influencing regeneration, provided a protein of good quality and of sufficient amount is also present in the diet.

It is of importance to determine whether, in addition to ridding the liver of fat during the preoperative period, it is possible to facilitate regeneration of hepatic tissue in the presence of ductal occlusion. It is now well recognized that in infectious hepatitis, as well as in homologous serum jaundice, degeneration and repair progress simultaneously.

Ferguson, Rogers and Vars[14] have studied the regeneration of the partially hepatectomized liver of the rat in the presence of common duct occlu-

sion. In some of the experiments the common duct was ligated some days before partial hepatectomy, and in others at the time of partial hepatectomy. The end-result has been essentially the same. Placed on an adequate dietary, the liver will regenerate, as can be demonstrated by an increase in hepatic cells (the presence of active mitoses persisting for even longer periods than would occur if the obstruction were not present) and an increase in hepatic cellular protein.

The conditions are not exactly similar to those found in man in the presence of common duct stricture or stone, for under the circumstances of their experiments cholangio-hepatitis did not exist. We have, however, now obtained evidence in man that regeneration can take place under conditions of recurrent cholangio-hepatitis (Figs. 5 and 6). Provided an adequate dietary is fed in the preoperative period, cellular repair and regeneration can be demonstrated in man by the presence of mitotic figures in liver specimens taken for study at the time of operation.

The demonstration that liver injury and repair can go on simultaneously in ductal occlusion and cholangio-hepatitis in a manner similar to that previously shown to occur in viral hepatitis gives new impetus to the vigor with which the preoperative dietary program should be pursued. While the influence of certain hormonal factors has been proved to be of definite help in the prevention of liver injury in the experimental animal and in its repair, no such relationship has been proved in man. It is, however, not unlikely that certain hormones may intensify the vigor of the repair which can now be induced by an adequate diet alone.

SUMMARY

It is more than probable that the reduction in functional capacity of the liver, which at times occurs subsequent to anesthesia and operation is due in large part to anoxia. This takes place during anesthesia from failure of an adequate oxygen supply. It may take place during operation from any condition which impedes blood flow to the liver, even when the circulating blood is well oxygenated, or from a reduced blood flow as occurs in shock. In the patient with suspected acute or chronic liver injury, the prevention of hepatic anoxia during and after operation is of major therapeutic importance to recovery.

A diet which is adequate in total calories and in composition will partially protect the liver from a wide variety of noxious agents and will facilitate repair of the liver damaged by these agents. It will even facilitate repair in the presence of recurrent cholangio-hepatitis in man. The importance of an adequate intake of protein, and of an optimal number of calories in the preoperative period, therefore takes on a new significance, for repair can be begun and functional capacity improved before the patient is subjected to the assault of anesthesia and operation.

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DISCUSSION.—DR. CALVIN M. SMYTH: There are two or three aspects of this very interesting presentation that I think might bear emphasis. The first of these has to do with the matter of the effect of anesthesia on the liver. If I heard him correctly, Dr. Ravdin said that the damage to the liver, even with some anesthetic agents usually considered innocuous, was dependent upon the length of time during which the liver was subjected to these periods of anoxia. I think that gives us a little pause to think, because it has become popular recently to measure the excellence of an operation by the time it took to perform it. I do not know whether that has impressed other people as it has impressed me, but it seems to me we hear about eight- and nine-hour operations which, because of the time it took them to perform, must be much better than the operation which took two or three hours to perform.

Now, I am not advocating the sacrifice of efficiency to speed. A lot of us were brought up in the "speed" era, and we know that it had many objectionable features. However, I would like to offer the thought to this body that if an operation can be performed efficiently in two hours, there would seem to be but little virtue in prolonging it for five or six, as I am afraid is done sometimes.

I was also very much interested in the point Dr. Ravdin brought out that liver destruction and liver repair could take place simultaneously, and that repair could take place even under conditions which, heretofore, have let us be sort of "horsed" into operating on patients we really didn't think were ready for operation.

It is a comforting thing to know—and have objective evidence such as was presented this morning—that these two things can go on simultaneously, even in severe cholangiohepatitis.

DR. OWEN H. WANGENSTEEN: The persistence and ingenuity with which Dr. Ravdin and his group have followed the problem presented by liver injury and repair has intrigued all surgeons; a debt of gratitude is owing Dr. Ravdin and his associates for the light which their studies have shed on factors which predispose toward, or guard against liver injury. While visiting Dr. Ravdin's clinic last fall, I had the pleasure of seeing the histologic picture of the diffuse necrosis of the liver which accompanies

gastric distention in the rat. It is startling. The liver is an important organ in helping the patient withstand the stress of formidable operations. We need only contemplate how poorly patients with cirrhosis tolerate surgery to remind ourselves of this fact. I have been learning something about this problem from another point of view.

When the Halsted Club met in Minneapolis last fall, I showed them a patient in whom I had excised the right lobe of the liver for metastatic cancer. Not knowing very much about how best to handle the problem at the time, and not wanting to spill too much blood, I put clamps on the vessels leading to the liver; Blalock clamps, snugly applied, were on the vessels for 33 minutes. This man, Mr. B. L., University Hospitals No. 796619, was a relatively young man (age 44) upon whom I was undertaking a somewhat delayed re-entry of his abdomen following a previous operation done a year before for an extensive gastric cancer. The only discernible evidence of recurrence was complete replacement of the right lobe of the liver with cancer; there was also a small recurrence over the upper surface of the left lobe. The temporary arrest of blood flow through the superior mesenteric, gastroduodenal and hepatic arteries, as well as the portal vein, afforded a completely bloodless field. The small metastasis in the left lobe was enucleated. The patient withstood the procedure nicely and convalesced satisfactorily.

Subsequently, I applied clamps to the same vessels in an older man, Mr. W. D., University Hospitals No. 812600 (age 59); in this instance, the flow through the superior mesenteric, gastroduodenal and hepatic artery and the portal vein was occluded for 24 minutes, during the excision of the left lobe of the liver and the left one-third of the right lobe. This man underwent a simultaneous total gastrectomy and excision of the distal end of his esophagus for an extensive gastric cancer. He remained somewhat oliguric for a few days, but convalesced satisfactorily. It was difficult to know whether the oliguria was owing to the arrest of blood flow through the liver or to the extensive surgery undertaken simultaneously.

Following this experience, I grew a bit timid and in another man, Mr. G. L., University Hospitals No. 801968 (age 59), for whom a delayed "second-look" operation was being undertaken almost a year following excision of a cancer of the left colon and enucleation of several nodules of metastatic cancer from the liver. I found it necessary on re-entry to deal again with hepatic metastases in both lobes of the liver. During the excision of the left lobe of the liver the Blalock clamps were applied to the same hepatic vessels, as in the 2 previous patients, for 12 minutes. Then the clamps were released for 20 minutes before partial excision of the right lobe was undertaken. For this latter procedure, the clamps were on an additional 15 minutes, with the free interval of uninterrupted blood flow for 20 minutes between. This patient did very well at operation. However, a few hours after operation, he became hypotensive, exhibited signs of confusion, and 20 hours after operation, death occurred. At operation, the liver had looked very well; at autopsy, the remaining liver was grossly very fatty. This man had been a chronic alcoholic for years. Obviously, in this instance, interruption of the arrest of blood flow into the liver did not protect the patient against hepatic anoxia.

Following the success of the first case, I asked one of my colleagues, Dr. Raffucci, to study this problem in the dog. Total arrest of inflow of blood to the liver is poorly tolerated in the dog, too, very few dogs surviving occlusions beyond 15 minutes, whether aureomycin or penicillin is given or not. Even interrupted arrest of blood inflow is poorly tolerated by the dog; on the contrary, interruption of the hepatic artery alone, as one would surmise, is well tolerated.

And when we learn more of the nature of liver injury and methods of protecting against it, and learn to master the technical problems of liver extirpation, another difficult hurdle in the advance of surgery will have been made. I am happy to be able to report here that, in a patient upon whom I undertook removal of the left lobe and

40 per cent of his right lobe for metastatic cancer last summer, a recent "second-look" operation shows the liver to be free of cancer. This is a heartening circumstance.

Following the loss of the patient from hepatic necrosis after interrupted application of clamps to the hepatic vessels, I abandoned all efforts at securing hemostasis in this manner during hepatic excision. Dr. Grafton Smith has built for me an instrument which can be applied over the structures within the gastroduodenal ligament to afford momentary hemostasis should it prove desirable. As yet, we have not studied how dogs tolerate that manner of interruption of blood flow.

In the extensive removal of liver metastases undertaken latterly in patients, I have approached the problem in a somewhat different manner. The problems confronting the surgeon in extensive removal of the liver essentially are the following: (1) hemostasis; (2) air embolism; and (3) biliary fistula. It would be nice to have a completely bloodless field; the experiences reported upon here, in man and in the dog, suggest definitely that arrest of flow of blood into the liver, other than momentary, is not practical. Moreover, in large excisions of liver tissue, the possibility of air embolism into the hepatic veins must be reckoned with. In the last few cases, I have done a median sternotomy, cutting out extra-plurally into the fourth interspace on the right side. A "T" bar to the left, if needed, affords excellent access to the stomach and esophagus. This maneuver brings the surgeon directly down upon the liver from above. After dissection of the suspensory ligaments of the liver, he can see the vena cava. It becomes relatively easy then to strip the liver tissue away from the ventral hepatic veins. They must be recognized and clamped before the surgeon cuts them to avoid air embolism. This technic of dealing with the problem results obviously in greater blood loss at the time of operation, but it avoids the problem of anoxia imposed upon the liver by even short periods of arrest of blood inflow to the liver.

Dr. Ravdin and his associates have approached the problem of hepatic anoxia from the broader standpoints of anesthesia and nutrition. This is an important problem; moreover, I think the studies of Dr. Ravdin's group and the technical considerations involved in the extensive excision of hepatic tissue have great importance for surgery. I believe the time is at hand when more surgeons will be embarking on such tasks. Liver does regenerate rapidly. I believe it will grow faster than cancer.

Dr. Everett I. Evans: I rise to discuss Dr. Ravdin's paper primarily because of its great importance to all of us—dietary care in the prevention and repair of the liver.

As you know, we are greatly interested in the burned patient, in whom—in practically every patient with a burn above 10 to 20 per cent—we find a moderate to severe liver damage, by all tests, on the fourth to sixth day.

I should say that aureomycin given at Hour 1, when the patient comes in—in large doses, has not seemed to show any protective influence against the liver damage following burns in man.

Secondly, we agree wholeheartedly with Dr. Ravdin on the importance of including fat in almost all diets given to all patients. First, diets without fat are practically impossible to eat. Secondly, that is the only method by which we can supply a proper caloric intake.

As an example of this importance in all burn patients, we are starting a complete diet on Day 1 of the burn, if they can take such a diet. We have found now in important studies being conducted by Dr. Levenson in our group that such burn patients with severe burns—that is, up to 30 per cent of the body surface—left the hospital in about five to eight weeks without a single pound of loss of body weight. Their diet contains a large amount of fat, so that even with liver damage which we know by test, fat included in a diet also containing large amounts of protein does seem to indicate the repair which, from Dr. Ravdin's paper, we know must be going on.

DR. I. S. RAVDIN (in closing): I should like to thank Drs. Smyth, Wangensteen and Evans for their discussions. I must say that I agree with Dr. Smyth. The anesthetist frequently cannot tell by looking at the lobe of an ear or the skin of the face whether the patient is or is not anoxic. The anesthetist must be constantly aware of the fact that the patient must have an adequate airway, and that a sufficient amount of oxygen is constantly provided the patient.

There are many factors concerned with relation of the blood supply to the liver in man as discussed by Dr. Wangensteen. I should point out that many years ago Dr. Ransahoff presented before this Association a paper on what happened to the blood pressure when the portal venous flow was impeded.

There are many abnormalities in the vasculature of this area and we frequently think we have ligated the major portion of the blood supply when, in reality, we have not.

I did not mean to infer for a moment that aureomycin solved many of the problems of hepatic insufficiency. I should like to call attention to the fact that at a meeting of the Armed Forces Epidemiological Board last fall, Dr. Stokes and Dr. Watson reported a group of patients in hepatic coma, in association with infectious hepatitis, in which recovery occurred following intensive aureomycin therapy. Just how that was brought about is not known, but anyone who has seen any large group of patients in hepatic coma, associated with infectious hepatitis, well knows that usually the mortality is nearly 100 per cent.

There can be no doubt but that one can, in certain instances, control the acute infection associated with cholangio-hepatitis in the presence of stone or stricture and then wait for a more reasonable period in which to do an operation of considerable magnitude.

POSTOPERATIVE SALT RETENTION AND ITS RELATION TO INCREASED ADRENAL CORTICAL FUNCTION*

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TEMPORARY DISTURBANCES of electrolyte and protein metabolism in the period immediately following a major surgical operation long have been recognized and investigated. The usual alterations in electrolyte metabolism include marked reduction in urinary excretion of sodium and chloride and a transient increase in the output of potassium. As a consequence of these electrolyte changes, water retention occurs. Because of this postoperative salt retention, saline solutions no longer are given routinely in the immediate postoperative period.[1] Moyer has summarized the electrolyte disturbances after operation and states that these changes cannot be attributed to alterations in renal blood flow, water deficit, sodium or chloride lack, blood loss or action of the anesthetic agent.[2]

A negative nitrogen balance independent of protein intake is also commonly encountered after operation. Amino acid solutions administered parenterally to counteract the excessive nitrogen excretion do not usually change the nitrogen balance significantly until about three or four days after operation.

It has been demonstrated that a major surgical procedure elicits a sharp increase in adrenal cortical function, as indicated by increased amounts of urinary excretory products which reflect steroids of the 11-oxysteroid and androgenic types.[3, 4] Actions of the 11-oxysteroids include, among other things, catabolism of body protein and depression of circulating lymphocytes and eosinophilic polymorphonuclear leukocytes. The fall in the number of circulating eosinophils provides a simple index of increased elaboration of these 11-oxysteroids.[5]

Since it might be expected that increased production of desoxycorticosterone-like steroids would occur simultaneously, it was decided to evaluate such activity. No direct measurement of changes in endogenous production of such electrolyte-regulating steroids is available. However, it has been demonstrated that the electrolyte composition of thermal sweat offers a reliable index of changes in the activity of these salt-active corticosteroids.[6] Analyses of sweat in various clinical and experimental conditions have shown an

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inverse relationship between desoxycorticosterone-like activity and the concentration of sodium and chloride in the sweat.[7] In the experiments described below, the electrolyte concentrations of serially obtained samples of sweat were used as an index of changes in the activity of the salt-active adrenal steroids.

METHOD

This method involves the collection of sweat from hands and forearms during a one-hour exposure of the entire body to humid heat (98° F. and 90 per cent relative humidity). Sweat samples were obtained from 14 patients before operation and at two- to three-day intervals after operation. In addition, a follow-up determination of sweat composition was obtained several weeks later on most subjects. Sweat tests are not performed at shorter intervals because of the possibility of inducing heat acclimatization, which is in itself a stimulus to adrenal cortical activity.[8] Electrolyte concentrations of sweat were determined by standard methods.[9] Some sodium and potassium determinations were also made with the flame photometer. Periodic eosinophil counts before and after operation were done by the method of Randolph.[10]

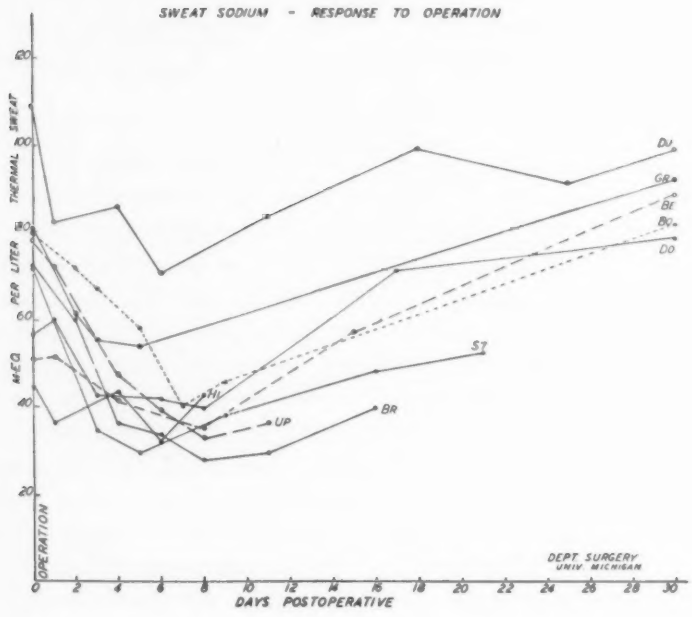
Twelve men and two women patients were studied by multiple sweat tests and eosinophil counts before and after operation. Ages ranged from 16 to 45 years, and the operations varied in severity from varicose vein ligations to subtotal gastric resections for chronic duodenal ulcer. Included were five gastric resections, three cholecystectomies, three herniorrhaphies, one splenectomy, one closure of colostomy and one varicose vein ligation. All subjects were excellent surgical risks, in good nutritional state, and none had malignant disease. Most received at least 5 Gm. of sodium chloride per day orally or parenterally during the postoperative period. Ether with nitrous oxide induction was the anesthetic usually used. Uneventful recovery followed in every case.

RESULTS

The results of sweat analyses before and following surgical operation are shown in Figures 1, 2, 3 and 4, and indicate increased endogenous production of salt-active corticosteroids after operation, as manifested by decreasing sodium and chloride concentrations of thermal sweat. The lowest values occurred five to eight days after operation, and represented average falls of 38.1 per cent in sodium (Fig. 1) and 39.0 per cent in chloride (Fig. 2). A gradual rise to the preoperative level then followed. A sharp rise averaging 73.3 per cent in the concentration of sweat potassium (Fig. 3) and 58.1 per cent in sweat nitrogen (Fig. 4) began on the first or second day and lasted for one or two days.

Quantitative determinations of circulating eosinophils on the same patients demonstrated increased 11-oxysteroid production, as indicated by a sharp decrease or complete disappearance of these cells within 12 hours after operation (Fig. 5). Between the second and fifth postoperative days the eosino-

FIG. 1



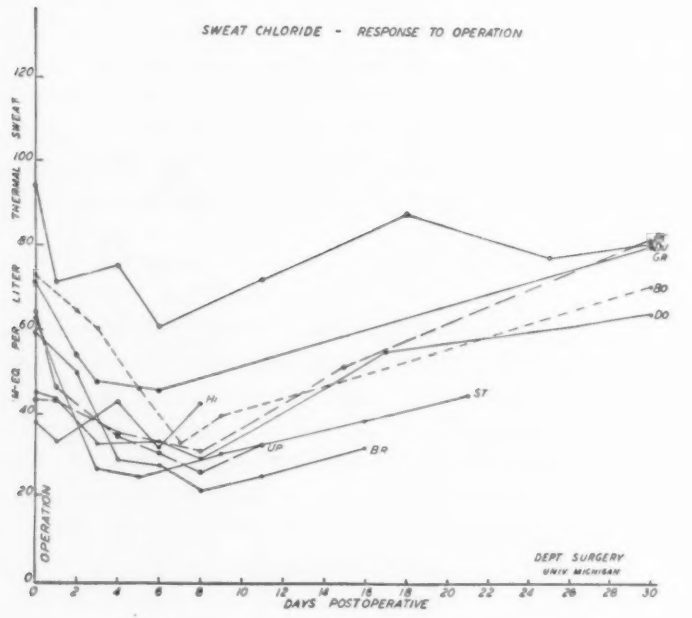
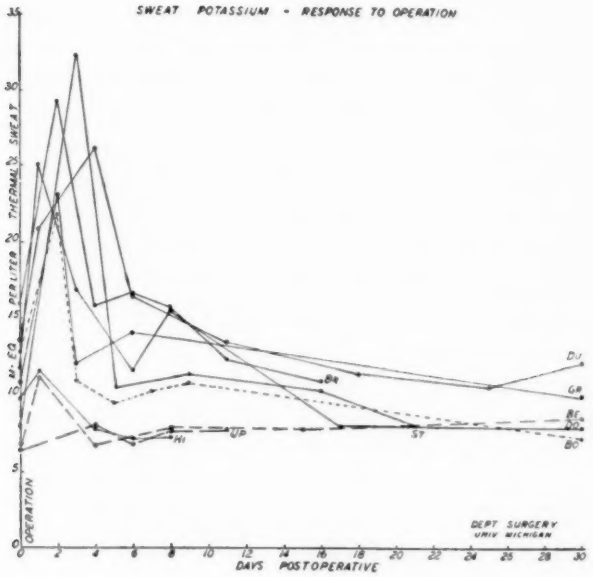


FIG. 2

FIG. 1.—Response to major operation of sodium concentration of thermal sweat.

FIG. 2.—Response to major operation of chloride concentration of thermal sweat.

FIG. 3



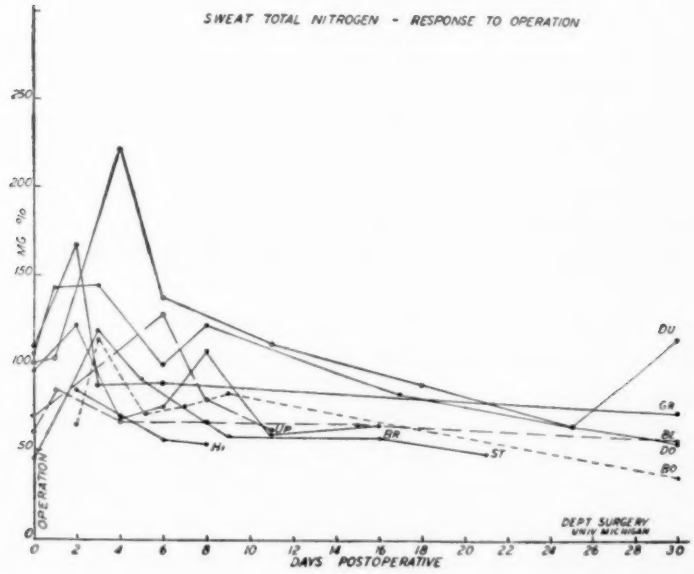


FIG. 4

FIG. 3.—Response to major operation of potassium concentration of thermal sweat.

FIG. 4.—Response to major operation of total nitrogen concentration of thermal sweat.

phils returned to the peripheral blood in numbers approximating or greater than the preoperative levels.

Figure 6 shows the typical changes in the composition of sweat as well as the changes in eosinophil and total leukocyte counts after operation. Characteristic of the desoxycorticosterone effect is the decrease in sweat sodium concentration of 30 per cent and a fall in sweat chloride concentration of 36 per cent.[8] An immediate but transient increase (114 per cent) in sweat potassium concentration occurs at the same time. With respect to the kidney, these two phenomena, sodium chloride retention and rise in potassium excretion, are now well established accompaniments of the postoperative state. They are equally well established effects of administered desoxycorticosterone.

Eosinophils disappear completely from the blood stream six hours after beginning the operation, and return to above preoperative levels five days after operation. An immediate rise in total leukocytes of the blood occurs as promptly but returns to the preoperative level gradually over many days.

Thirteen of the 14 patients studied demonstrated a significant fall in sodium and chloride concentrations of thermal sweat. One subject, a 42-year-old male, who underwent repair of a recurrent inguinal hernia, failed to show the characteristic electrolyte changes and maintained relatively constant sweat composition. His eosinophil response also was one of the least marked of the group. His postoperative course, however, was uneventful.

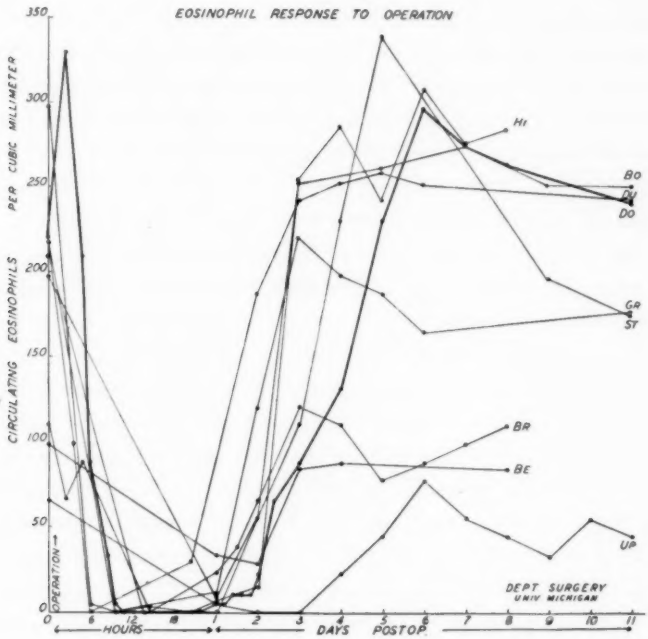
DISCUSSION

Recently it has been shown[6] that stimulation of the adrenal cortices of normal people results in the appearance of metabolic changes which reflect increased activities of three main types of adrenocorticosteroids, namely, electrolyte-regulating or 11-desoxycorticosterone-like steroids, 11-oxysteroids, and steroids having activities and end-products characteristic of sex hormones. The latter two groups already have been shown to be increased following operation.

1. *Effects of 11-Desoxycorticosterone-like Steroids.* Desoxycorticosterone administration to normal persons produces marked reduction in urinary excretion of sodium, chloride and water.[11] This effect continues only for two or three days, and is followed by a rebound of urinary sodium and chloride output to levels even higher than normal, despite continued desoxycorticosterone administration.[8] Increased extracellular fluid and plasma volume accompany this retention. This steroid also causes increased renal excretion of potassium, but has little or no effect upon protein or carbohydrate metabolism or upon circulating leukocytes. While the electrolyte composition of the urine may be a good measurement of deficiency of salt-retaining corticosteroids, it is a poor indicator of increased activity of these desoxycorticosterone-like compounds because of the renal "rebound" phenomenon.

The electrolyte composition of sweat reflects activity of electrolyte-regulating steroids. Changes in the composition of sweat have been followed in

FIG. 5



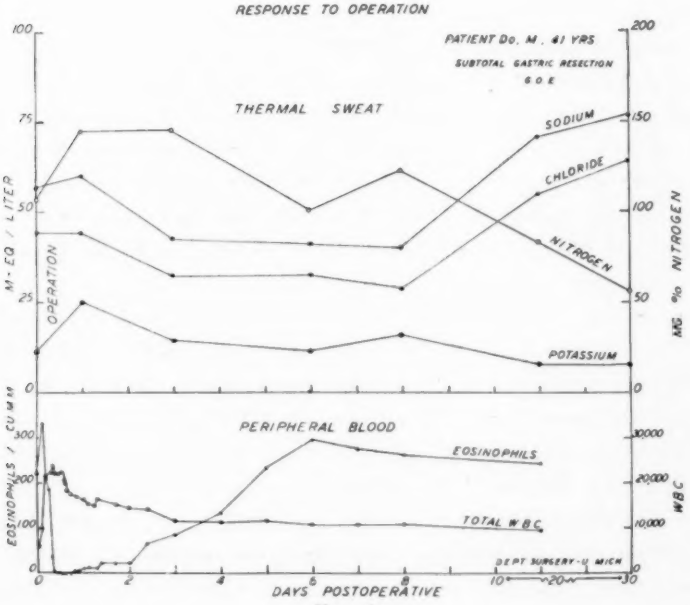


FIG. 6

FIG. 5.—Response to major operation of circulating eosinophils in peripheral blood.

FIG. 6.—Response to sub-total gastric resection of electrolyte concentrations of thermal sweat, and circulating eosinophils and total leukocytes of the peripheral blood. The patient is a 42-year-old male operated upon for chronic duodenal ulcer.

various conditions exhibiting abnormal adrenal function.[7] Patients with untreated Addison's disease or adrenal insufficiency show sodium and chloride levels in thermal sweat greatly in excess of normal values. On the other hand, conditions associated with hyperactive adrenal cortices such as Cushing's syndrome demonstrate sweat sodium and chloride values below normal levels. Even lower concentrations of these electrolytes in sweat are found in adrenal cortical carcinoma.

Sweat composition patterns similar to those observed in adrenal cortical hyperactivity may be produced by administration of desoxycorticosterone. Coincidental with the sharp renal retention of sodium and chloride after injecting the steroid in normal people, the sweat concentration of these electrolytes falls. However, although the kidney resumes excretion of sodium and chloride in three or four days despite continued desoxycorticosterone administration, the sweat glands continue to secrete a fluid low in sodium and chloride as long as the steroid is given. It is for this reason that the electrolyte composition of sweat affords a more reliable index of electrolyte-regulating corticosteroid activity than does the renal excretion of sodium and chloride. We believe that the data presented above afford adequate evidence of increased activity of salt-active adrenal steroids in the postoperative period.

2. Effects of 11-Oxysteroids. A second type of steroid, characterized by an oxygen atom or a hydroxyl group at the carbon-11 position of the steroid molecule, has its major physiologic effects upon organic metabolism (protein, carbohydrate and fat). Catabolism of body protein and depression of lymphocytes and eosinophils are among the actions of these 11-oxysteroids.

Increased 11-oxysteroid production in Cushing's syndrome, in some cases of adrenal cortical carcinoma, and following trauma or operation, has been demonstrated by analysis of urinary excretory products.[3] It has been established by metabolic studies that following operation or injury to a previously healthy individual, there is an increase in catabolism of body protein with a marked rise of urinary nitrogen. Coinciding with this period of negative nitrogen balance is a six to tenfold increase in the excretion of urinary 11-oxysteroids, as measured by the glycogen deposition test.[12] Five days after hysterectomy the value returned to the preoperative level.[13] It has been observed that debilitated or carcinomatous patients respond to trauma with little or no increased excretion of nitrogen, and that the usual rise in corticosteroid output may be absent or transient.[14]

The administration of 11-oxysteroids to hypoadrenal patients is followed by marked depression of circulating eosinophils in the peripheral blood, and operative procedures have been shown to cause sharp reduction of these cells in animals.[15] Roche *et al.*[16] recently have reported that there is almost complete disappearance of eosinophils within one or two days after a major operation in previously healthy individuals, and that nondisappearance of these cells within two days after operation may indicate a lack of the normal adrenal cortical response to operation. A lymphocyte depression after stress

also has been described and shown to be dependent upon increased 11-oxysteroid activity.[17, 18] A rise in circulating neutrophils is produced by 11-oxysteroid administration.

3. Androgenic and Estrogenic Steroids. A third group of steroids with androgenic or estrogenic properties is believed to be elaborated by the adrenal cortex. These may be measured by determination of their urinary excretory products in the form of 17-ketosteroids (androgenic) and estrogenic substances. In healthy men a transient rise in urinary 17-ketosteroids is observed following operation, but this response is minimal in debilitated patients.[4]

Our data from the experiments reported above supplement that which previously has been known, in that they demonstrate the participation of increased activity of electrolyte-regulating steroids in the immediate postoperative period. They explain at least in part the capacity of the patient after operation to retain abnormally large quantities of sodium and chloride and to excrete large amounts of potassium.

Since the entire metabolic picture exhibited by the postoperative patient can be duplicated in healthy individuals by injections of anterior pituitary adrenocorticotrophic hormone (ACTH)[6, 19] it is now evident that a major surgical procedure constitutes an "alarming stimulus"[20] in man.

CONCLUSIONS

1. A major surgical procedure constitutes an "alarming stimulus" in man, resulting in increased elaboration of pituitary ACTH with a resultant increase of adrenal cortical activity during the first five to nine days after operation.

2. Studies of the changes in the composition of thermal sweat before operation and periodically after operation indicate that in the immediate postoperative period there occurs increased activity of those adrenal steroids which produce retention in the body of sodium, chloride and water.

3. It is concluded that increased elaboration by the adrenals of desoxycorticosterone-like steroids accounts, at least in part, for salt retention and the accompanying potassium diuresis after operation.

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Discussion.—Dr. Jonathan E. Rhoads: At the University of Pennsylvania we have puzzled for a long time over the oliguria so frequently seen after major operations during the first day or two, and we were greatly interested and impressed by the presentation of Dr. Conn at a meeting of the Society of Clinical Surgery at Ann Arbor about a year ago, relating this phenomenon to adrenal cortical function.

Dr. James Hardy in our clinic has also employed the method of Thorne to correlate adrenal cortical activity with the change in fluid balance following extensive surgical operations. The eosinophil count and the fluid output followed a similar course after operation. This is in agreement with the data which has just been presented.

Dr. Hardy believes that the course of the eosinophil count may be of some prognostic value, because it was the impression that in patients with advanced malignancy,

and patients in generally poor condition, the eosinophil count recovered more sluggishly following operation. The volume of the gastro-intestinal secretions was often diminished in the early postoperative period also. Therefore, there need be no cause for concern when the volume of Miller-Abbott tube drainage is small, so long as the abdomen remains soft and flat. It seems clear that the adrenal cortex plays a significant and important role in the postoperative retention of salt and water.

I certainly wish to congratulate Dr. Coller, Dr. Johnson and Dr. Conn on this excellent addition to surgical physiology, and upon the test of electrolytes in perspiration which they have used further to elucidate this problem.

DR. FRANCIS D. MOORE: I would like to thank Dr. Conn, Dr. Coller and Dr. Johnson for their very beautiful piece of work, adding another chapter to this rapidly growing volume on the relation of the adrenal cortex to surgery.

I would like to mention just one or two findings that we have made in our laboratories which go along with and may, in a small way, round out some of their observations. In the first place, it is almost impossible to quantitate the milligram equivalence of an operation in terms of ACTH by hospitalizing normal individuals and studying their salt picture after giving ACTH and comparing it with various operations. We find that 100 to 150 mg. of ACTH over a two-day period corresponds roughly to the alarm reaction of a subtotal gastrectomy. This is, as you can well imagine, a big stimulus in terms of ACTH.

We have noticed, just as Dr. Johnson has, that the eosinophiles come back before the sodium-potassium trade has completed. This is interesting evidence of the disassociation of these two actions of two of the adrenal hormones.

As correlative evidence, it is interesting that a second trauma within ten days of the first trauma will drop the eos but will not produce the electrolyte effect. To us this is very significant with regard to the old clinical observation that the second stage of a two-stage operation (carried out seven to 14 days later) elicits a somewhat different clinical response from the initial procedure.

It is also interesting that prolonged continuation of ACTH—as has been shown by Dr. Thorn and his group—produces at first the Na-K shift, but then, after about a week, even though the ACTH is continued, Na and K come back into line. As far as practical therapy is concerned, it doesn't seem necessary to replace the potassium unless there is a change in acid-base balance which will alter the plasma potassium concentration. However, avoidance of sodium, as has been shown so beautifully by Dr. Coller, Dr. Moyer and their group, is of great importance unless there are extrarenal sodium losses over which the adrenal cortex has no control.

DR. BERNARD ZIMMERMAN: I thought this was a very excellent demonstration of the importance of the adrenal cortex, and the fact that the salt retention following surgery is generalized phenomenon and one that is not restricted to the kidney.

We have also been interested in some of these phenomena following surgery, particularly in the correlation of the eosinophil count with the alarm reaction. We have observed, as others have, that there is a pronounced drop in the sodium and chloride concentrations in the serum immediately after surgery. In general, they return to normal somewhere around the same time that the eosinophils do. However, a couple of instances have made us feel that there is no real relationship here, but rather that the action of the adrenal as indicated by the eosinophil count is a compensatory response to prevent other changes, traumatic changes which occur in the body, and this is what one would expect from the original work of Selye and Browne, which showed that in the initial stages of the alarm reaction, there was oliguria, hypochloremia, and a tendency to the retention of water.

[Slide] This slide shows the sort of thing we sometimes see. We have noticed in several patients who have been studied by Dr. Ariel—who spent a year at the University of Minnesota—that in the very early postoperative stage there is a tendency to retention of water, and we have had some instances with the development of apparent water intoxication, with convulsions.

This is such a patient. Notice that on the second day after operation, his eosinophils were normal. He was an elderly patient, and had a very extensive operation—as you see here, a gastrectomy, with partial pancreatectomy and excision of a portion of the colon.

It is anomalous in our findings to have the eosinophils back to normal the second day after such an extensive operation. You will see that his chloride and sodium were extremely low at that time, and at that time he developed convulsions. Then his eosinophils began to come down again, and he was unconscious for two days; then he returned to normal and was perfectly all right.

In this instance we have a disparity between the eosinophils and the chloride, and we feel that he must have had some sort of transient adrenal failure postoperatively.

Dr. Moore mentioned evidence for separable functions of the 11-oxy substances, and the desoxy or salt-retaining substances. We have been particularly intrigued by the work of Greep on rats, in which it was shown that the administration of ACTH did not provoke the excretion or the liberation of desoxycorticosterone-like substances. There is evidence, of course, that such is not the case in the human being, because both surgical operations and administration of ACTH cause transient sodium retention.

We were interested in investigating the possibility of the separable functions of these two substances in the human being, and we wanted to know whether exposing the human being to a situation which would demand the production of a large amount of desoxycorticosterone-like substances would involve the pituitary and the release of ACTH.

[Slide] The next slide shows figures on patients who were subjected to a very abnormal situation, with low sodium intake—around ten to 13 m/eq. per day, and a very high potassium intake; up to 250 or some m/eq. per day. The situation must impose a considerable stress on the adrenals; certainly a patient with Addison's disease would respond very poorly to such a regime. However, you will notice the eosinophil counts which were done daily on such patients.

The underlined values on the end indicate the controls, or counts after the subjects had been on a normal diet for 24 hours. You see that there is no depression of the eosinophils. As a matter of fact, there is a slight increase in the early part of the experimental period.

Similarly, we are interested in whether the exposure of the human subject to such a regimen would increase the output of the 11-oxy type of substance.

[Slide] The next slide shows both eosinophils and corticoids on three such subjects. These are so-called formaldehyde-producing corticoids, in this instance representing oxycorticoids, because we have pretty good evidence that desoxycorticosterone is not excreted as such in the urine.

You will notice that in at least two of the cases there is a pronounced fall in the output of the oxycorticoids in the urine, and probably a slight, probably not a significant fall in the third patient, but at least there is no increase.

Likewise, the eosinophils are plotted here, and there seems to be a transient increase in the initial phase of the experiment, so this at least indicates that the activity of the pituitary may not be important in the response of the adrenal to "electrolyte" stress. However, this does not eliminate the possibility that production of ACTH may cause the release of desoxycorticosterone-like substances, but at least we know they can be separable.

The possibility has occurred that maybe desoxycorticosterone-like substances are not necessary, for Thorne has shown in Addison's disease that Compound E, for example, will cause sodium retention.

Likewise, in the recent report of Sprague and Kendall and the group at Rochester, Minnesota, it was shown that large doses of Compound E, which is an oxycorticoid, would cause sodium retention quite similar to that of ACTH, so I suggest that it may be possible that the salt-retaining features that we see following the administration of ACTH in surgical patients could be the result of the same hormones which cause changes in the nitrogen metabolism, rather than the desoxy group.

DR. FREDERICK A. COLLER (in closing): As Dr. Johnson said, this paper is largely confirmatory of the work of others, and in the body of the paper, as published, due credit, of course, will be given to all of those who have helped us so much.

I would like to emphasize again our debt to the other author, Dr. Conn, whose technical knowledge, and whose development of the sweat test, which shows a definitive electrolyte pattern in response to the administration of ACTH, has been all important to this little study.

I think that something really very constructive can be drawn from this. It is rather clear that these chemical changes that have been mentioned are exaggerated with the length of the operation and with the magnitude of the operation.

There is a rather common habit, in many clinics and operating rooms, to start the fluid going (I hope it is only water—that is, a glucose solution) and let it run at least until the end of the operation. Now, if an operation lasts an hour, the patient will tolerate this really very well, but if it lasts seven or eight hours, as they sometimes do, you are piling water into a patient who, as the hours go by, can manage this very much less efficiently. I am sure that if one plans to carry out long operations, one should be very thoughful about this point and limit the amount of glucose solution, or salt solution, because most water and salt will not be eliminated in the normal manner if the operation has been a long one. So let us plan on giving the appropriate amount of fluid, and then stopping. Let the anesthetist seek some other avenue in which to give his many drugs.

In conclusion, I will thank those who were good enough to discuss the paper—Dr. Rhoads, Dr. Moore and Dr. Zimmerman—and I repeat what I said a number of times lately, that I feel the principal function of my afternoon round is to separate the patient from the bottle that is hanging over his head, by pulling out the needle.

STUDIES OF COMBINED VASCULAR AND NEUROLOGIC INJURIES

I. THE EFFECT OF SOMATIC AND SYMPATHETIC DENERVATION UPON THE RESULTS OF ARTERIAL LIGATION IN THE RAT*

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DIFFICULT AS ARE THE PROBLEMS of sudden traumatic interruption of continuity of important arteries on the one hand and of injuries to large peripheral nerves on the other, combined neurologic and vascular injuries are even more trying. The extensive damage which may result from such injuries and the difficulty of achieving good anatomical and functional restoration present some very puzzling features. That a decrease in blood flow should affect adversely the neurologic component is understandable from the consideration of the neurologic damage which sometimes results from ischemia alone. Somatic denervation, however, especially during the first few weeks, is generally thought to increase, rather than to decrease, blood flow to the affected area and hence might be expected to minimize rather than to exaggerate the tissue damage resulting from ischemia. Such considerations and other unsolved related problems have prompted us to undertake a broad experimental study aimed at better understanding of the nature of the alteration resulting from combined neurologic and vascular injuries, of the effects of somatic and sympathetic denervation alone and combined upon blood flow and general nutritional status of the extremity, of the influence of circulation upon the regeneration of peripheral nerves, as well as of the general problem of ischemic paralysis and the concept of trophic disturbances. Our initial observations are reported in the present communication.

MATERIALS AND METHODS

Domestic albino rats weighing from 100 to 150 Gm. were used. Operations were performed with relatively clean but not aseptic technic. The animals were anesthetized by the intraperitoneal administration of pentobarbital sodium, .033 Gm. per Kg. of body weight. The arterial injury consisted of the division between fine silk ligatures of the left common iliac and common femoral arteries. A transperitoneal approach was used for exposure of the iliac artery. The neurologic injury consisted of the complete division of all the fibers of the left sciatic nerve, performed according to the technic of Denny-Brown.[1] The nerve was exposed in the buttock by splitting the fibers of the gluteus muscles. A longitudinal incision about 4 mm. in length was

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made in the sheath of the nerve and, with the aid of a dissecting microscope, all the fibers were sectioned; the incision in the sheath was not sutured. Sympathectomy was performed transperitoneally; the chain was resected from the level of the left renal vessels down to the level of the bifurcation of the aorta. The abdominal muscles and fascia were closed with a continuous suture of 0000 silk, the skin with Michele clips.

The sympathectomy and the arterial ligations were always performed at the same operation. Division of the sciatic nerve was carried out in one series two or three days after the arterial ligation and in another from three to five weeks beforehand. Immediately after operation dilute picric acid solution was applied to the left hind extremity of those animals in which the sciatic nerve was sectioned. This treatment appeared to be effective in preventing the animals from chewing their anesthetic limb. The same picric acid solution

TABLE I.—*The Effect of Ligation and Division of the Left Common Iliac and Common Femoral Arteries and of Treatment by Left Lumbar Sympathetic Ganglionectomy. Results Three Months After Ligation.*

Number of Animals	Treatment	Animals Without Paralysis or Gangrene		Animals With Paralysis But Without Gangrene		Animals with Gangrene			
						Number With Loss of Tissue Limited to Toes	Number With More Extensive Loss of Tissue	Total	
		Number and Per cent	Diff: S. E. Diff.	Number and Per cent	Diff: S. E. Diff.			Number and Per cent	Diff. S.E.Diff.
26	None	13 (50)		11* (42)			1	1 (4)	
29	Sympathectomy	23 (79)	2.34	3 (10)	3.96	†	2	3 (10)	0.95

* One additional rat with paralysis was sacrificed one month after ligation because of middle ear disease.
† One rat with gangrene of a single toe was sacrificed two months after ligation because of emaciation.

was also applied to the ischemic limb of a number of rats after simple arterial ligation in order to make certain that the solution itself would cause no damage; no harm resulted. All the animals were observed carefully at frequent intervals and notes were made concerning the presence or absence and degree of paralysis and gangrene. The rats were maintained on a diet of commercial dog pellets and water. An autopsy was performed upon each of the few animals which died during the course of the study.

RESULTS

Immediately after the arterial ligation was performed the corresponding foot appeared very pale and was palpably colder than the contralateral foot. In those animals which recovered promptly without paralysis or gangrene the initial pallor and coldness disappeared rather rapidly and often was not evident the day after operation. On the other hand, those animals in which necrosis of tissue developed, or in which paralysis continued for a period of time, tended to have persistence of some pallor for several days. When arterial ligation and sympathetic denervation were carried out simultaneously

the same coldness and pallor were evident immediately after operation but in general tended to disappear more rapidly than in the other group.

The effect of sympathetic ganglionectomy upon the injury resulting from arterial ligation is illustrated in Table I. In the case of those animals in which the arterial injury alone had been inflicted, 13 of the 26 extremities (50 per cent) had, by the end of three months, recovered to such an extent that they appeared entirely normal. There was no loss of tissue and no evidence of motor difficulty. The animals could flex and extend the ankle and toes and spread the toes normally. The results were considerably better in the group in which sympathetic denervation was carried out simultaneously with the arterial ligation; 23 of the 29 animals, or 79 per cent, had escaped without injury or had recovered completely. There was no significant difference in the incidence of gangrene in the two groups.* Gangrene resulting in loss of more tissue than toes had occurred in one rat in the group subjected

TABLE II.—*Ischemic Paralysis Following Arterial Ligation and the Influence of Sympathetic Denervation Upon Rate of Recovery of Function.*

Interval After Arterial Ligation	Arterial Ligation Alone (26 rats) Number and Per cent Without Paralysis or Gangrene	Arterial Ligation and Sympathectomy (29 rats) Number and Per cent Without Paralysis or Gangrene	Diff.: S. E. Diff.
3–4 days	3 (11.5)	5 (17.2)	
1 week	3 (11.5)	12 (41.5)	3.08
1 month	7 (26.9)	20 (68.9)	3.44
2 months	10 (38.5)	23 (79.3)	3.38
3 months	13 (50)	23 (79.3)	2.34

to arterial ligation alone and in two rats in the group treated by sympathectomy. One additional rat in the latter group had gangrene of a single toe at the time it was sacrificed because of weight loss two months after operation.

The difference in the two groups in the rate of recovery from the ischemic paralysis which occurred so commonly early after arterial ligation is evident in Table II. On the third or fourth day after operation 17.2 per cent of those treated by sympathectomy had no gangrene and normal motor function and this was the case in 11.5 per cent of those subjected to arterial ligation alone. By the end of one week the percentages were 41.5 and 11.5 respectively, by the end of one month 68.9 and 26.9, by the end of two months 79.3 and 50. The differences in these percentages are statistically significant. The characteristic posture of the paralyzed as compared with the normal hind extremity is illustrated in Figure 1.

When sciatic nerve section alone was carried out, complete paralysis of the foot followed and in six of 29 animals some loss of tissue was sustained (Table

* All the data were analyzed statistically by dividing the difference between the proportions by the standard error of the difference of the proportions. Values greater than 2 are indicative of statistical significance. A value of 2.5 indicates that the result could be produced by chance alone once in 81 times, a value of 3 only once in 369 times.

III). When division of the sciatic nerve was preceded a few days beforehand by arterial ligation the incidence of loss of tissue was very much higher. Indeed, gangrene involving the toes was present in 16 of the 26 animals while in seven additional animals more extensive gangrene developed. When sympathetic ganglionectomy was carried out in addition to the arterial and sciatic nerve injury, the loss of tissue was strikingly reduced. Some gangrene of toes developed in eight of 23 animals, but only one sustained more extensive loss of tissue. The incidence of extensive gangrene was actually less than in the control group with sciatic division and normal blood supply, though the difference is not statistically significant. Indeed, the total incidence of gangrene in these two groups does not differ significantly. On the other hand, the incidence of extensive or minimal gangrene occurring in those animals in which an arterial and a somatic nerve injury was inflicted without sympathetic ganglionectomy was significantly higher than in either one of the other two groups. Varying degrees of loss of tissue are illustrated in Figure 2.

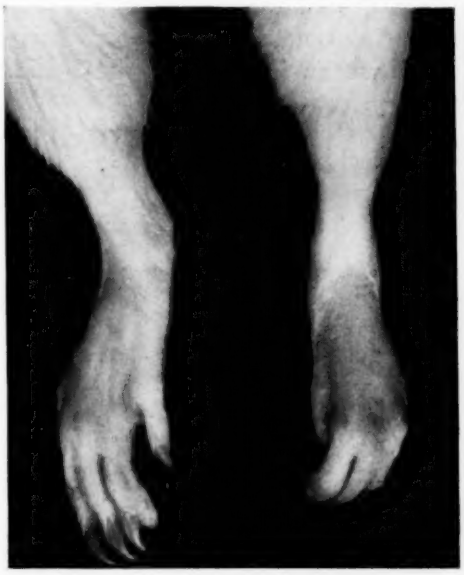

FIG. 1.—Photograph illustrating characteristic posture of paralyzed extremity. This rat had undergone arterial ligation four months previously.

TABLE III.—*Gangrene Following Ligation and Division of the Left Common Iliac and Common Femoral Arteries and/or Section of the Left Sciatic Nerve and the Effect of Treatment by Immediate Left Lumbar Sympathectomy. Results Two Months After Ligation or Sciatic Section.*

			Animals With Gangrene		Total	
Injury Inflicted	Treatment	Number of Animals	Number With Loss of Tissue Limited to Toes	Number With More Extensive Loss of Tissue	Number and Per cent	Diff.: S. E. Diff
Sciatic section	None	29	3	3	6 (20.7)	
Arterial division and sciatic section	None	26	15*	7	23 (88.6)	6.84
Arterial division and sciatic section	Sympathectomy	23	8	1	9 (39.1)	1.46

* One additional animal which died one month after operation had gangrene of toes.

In Table IV are compared the results with regard to loss of tissue following arterial injury inflicted approximately a month after sciatic nerve section with that sustained when the sciatic division was performed within a few days after arterial ligation. Extensive gangrene occurred more commonly in the

first group, though the differnce is not statistically significant. The incidence of minimal gangrene and the total incidence of gangrene was significantly greater in the group in which the nerve injury was inflicted a few days after the arterial injury.

There has been no recovery of neurologic function following sciatic nerve section during periods of observation as long as one year in any animal which was subjected to arterial ligation as well.

DISCUSSION

The experiments reported demonstrate that in the rat, as is apparently true in man, much more serious damage results from combined neurologic and vascular injuries than from either one alone. Loss of tissue from necrosis

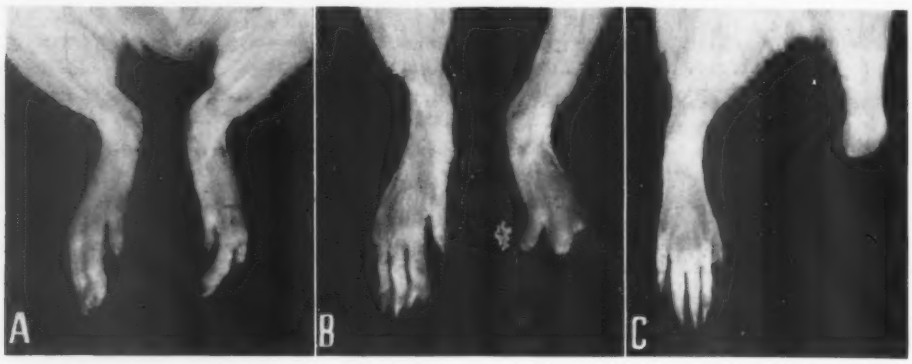

FIG. 2.—Photographs illustrating varying degrees of loss of tissue following arterial and somatic nerve injury.
A. Complete loss of fourth and fifth and partial loss of third toe.
B. Partial loss of first and second and complete loss of other three toes as well as of lateral portion of the distal metatarsal area.
C. Complete loss of foot.

occurred in only 4 per cent of those animals subjected to arterial ligation alone, in 21 per cent of those in which a sciatic injury was inflicted, and, in contrast, in 89 per cent of those with combined neurovascular injuries. In addition, though ischemic paralysis was very common after arterial ligation, 50 per cent had made a complete recovery by the end of three months. Similarly, in other studies[2] complete functional return occurred in from 88 to 164 days after actual excision of a few millimeters of all the sciatic nerve fibers with preservation of the sheath. On the other hand, though some of them have been observed for periods as long as one year, no animal with the combined neurovascular injury has recovered neurologic function.

It is understandable that the regeneration of a divided somatic nerve should be influenced adversely by diminution in arterial blood supply to the limb, since the integrity of function of intact somatic nerves is so dependent upon adequate circulation. Transient loss of nerve function in instances of episodic ischemia, such as attacks of Raynaud's phenomenon, and more or less permanent damage to peripheral nerves in instances of persistent ischemia,

such as that following thrombosis of important arterial stems, are observations which have been made repeatedly. Similarly, the sensitivity of the peripheral nerves of the rat to deprivation of blood supply is evident from the high incidence of ischemic paralysis which followed ligation of the common iliac and common femoral arteries.

It will obviously be important to find out more about the relationship between ischemia and its interference with nerve regeneration and about possible facilitation of regeneration in such circumstances by measures which improve blood flow. In the experiments reported, even though sympathetic denervation minimized tissue necrosis, it did not demonstrably enhance the return of nerve function. Studies with lesser degrees of circulatory impairment are being initiated in an effort to inquire further into these relationships. It is also important to know what gross anatomical and histologic changes

TABLE IV.—*Comparison of Loss of Tissue Following Arterial Injury Inflicted Three to Five Weeks After Sciatic Section and That Sustained When Sciatic Section Was Performed Two or Three Days After Arterial Ligation. Results One Month After Arterial Ligation.*

		Gangrene					
		Loss of Tissue Limited to Toes		More Extensive Loss of Tissue		Total	
Injury Inflicted	Number of Animals	Number and Per cent	Diff. S. E. Diff.	Number and Per cent	Diff. S. E. Diff.	Number and Per cent	Diff. S. E. Diff.
Sciatic followed by arterial	19	2 (10.5)		9 (47.4)		11 (57.9)	
Arterial followed by sciatic	26	18 (69.3)	4.9	7 (26.9)	1.43	25 (96.2)	3.2

may be associated with delayed or absent return of nerve function in the presence of ischemia. Such studies are also being carried out.

If the influence of ischemia on the regeneration of somatic nerves and paralysis resulting from circulatory insufficiency are understandable, it is equally difficult to comprehend the apparent tendency for deprivation of somatic nerve supply to increase the necrosis of tissue in limbs subjected to arterial injury. It is well known that anesthetization of a somatic nerve is attended by an increase in circulation in the anesthetic area as measured by skin temperature and digital plethysmographic studies, even though the induced vasodilatation falls somewhat short of that which can be effected by sympathetic nerve block. Similarly it is known that complete division of a somatic nerve is followed by a warm phase which generally lasts about three weeks, though the period of time varies considerably from one case to another. In the cold phase which follows, to be sure, the circulation tends to be reduced in the denervated area. Yet one might reasonably speculate that complete division of a peripheral nerve should have the initial effect of, at least in a sense, counteracting the circulatory impairment resulting from a

concomitant arterial injury and thus of reducing the hazard of gangrene. Yet such does not appear to be the case; certainly not in the experiments reported. From what is known of the circulatory response to complete somatic denervation of an area one might anticipate that if an arterial injury occurred late after division of a peripheral nerve, during the cold phase, the effect might be one of enhancing the tissue loss. Peculiarly enough, however, in our preliminary observations in the rat, tissue loss tended to be greater when the sciatic section was done a few days after the arterial ligation rather than three to five weeks earlier.

In attempting to explain the later cold phase after complete somatic denervation, the factors which have been judged of chief importance[3, 4] are the lowering of local metabolism, the sensitization of denervated blood vessels to circulating adrenalin, and loss of afferent fibers necessary for the so-called "axonal vasodilatation" of Lewis. At least the latter alteration is dependent upon nerve degeneration. It is apparent that studies similar to those reported in this communication should be extended to other species, should include nerve injuries inflicted at various levels, cord, roots, trunk, etc., and should include objective study by all available methods of the circulation in these various circumstances. It is our hope to complete such a program of investigation.

Perhaps the most surprising observation in this current study, in the light of generally accepted knowledge, is the benefit of sympathetic ganglionectomy in preventing tissue necrosis in the ischemic and somatically denervated extremity. The observed benefit of sympathectomy after simple arterial ligation would be anticipated according to all available information, since sympathectomy has been repeatedly demonstrated in man and in experimental animals to be of potential aid in improving the circulation under such circumstances. Many have held the view, however, that the blood flow to a completely denervated area could not be improved by sympathectomy, since presumably all sympathetic impulses to the anesthetic area have already been interrupted. If one considers the factors previously mentioned as being possibly of greatest importance in initiating and maintaining the cold vasomotor phase of somatic denervation, it is clear that the addition of sympathectomy would hardly alter any one of them, neither the lowered local metabolism, the sensitization of the vessels to circulating epinephrine, nor the loss of axonal vasodilatation because of interruption of afferent nerve fibers. There is, however, another factor which has been thought to be of considerable importance by some[3] and of little importance by others,[4] namely, the integrity of innervation of the rest of the limb. Those who feel that this factor is important maintain that the normal capacity of the non-paralyzed portion of the extremity to undergo vasoconstriction as a response to such stimuli as a cold environment results in a net decrease in blood flow to the denervated area. It is our feeling that this consideration is very important in understanding the benefit of sympathetic interruption in a limb already rendered anesthetic in

part by peripheral nerve division. It[5] has been emphasized previously that a marked increase in oscillometric readings may be observed after sympathectomy in extremities in which the surface temperature had previously been high and relatively stable as a result of somatic anesthesia. It would seem that our present studies, coupled with comparable clinical experiences, will necessitate serious consideration of sympathectomy as wise treatment in relatively ischemic extremities even though, and perhaps indeed all the more because, somatic anesthesia is present.

SUMMARY AND CONCLUSIONS

1. Experiments are reported demonstrating that ligation of the common iliac and femoral arteries in the rat is followed by a low incidence of gangrene, but a very high incidence of ischemic paralysis. Immediate sympathectomy is effective in hastening recovery from this ischemic paralysis.

2. When arterial ligation is combined with section of the sciatic nerve, recovery of nerve function is markedly delayed and the occurrence of tissue necrosis is strikingly increased. Sympathectomy effectively reduces the incidence of necrosis of tissue.

3. The possible significance of these observations is discussed and promising avenues of future investigation are outlined.

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DISCUSSION.—DR. GEORGE E. STOKES (in closing): It is our feeling that perhaps the chief value of the studies reported tonight lies in the extension and expansion of these studies according to avenues which appear to be important and potentially fruitful. It is our plan to broaden our investigations in an effort to clarify some of the following incompletely understood problems.

First, the effect of somatic and sympathetic denervation—alone and combined—upon blood flow and nutrition of the extremity.

Secondly, the influence of varying degrees of ischemia upon the regeneration of peripheral nerves, and of possible methods of influencing favorably nerve regeneration in such ischemic limbs.

Third, better understanding of the general problem of ischemic paralysis and of the pathologic alterations which accompany it.

And, finally, the general concept of the so-called trophic disturbances.

For more exact information about the circulation it is apparent that larger animals than rats will be required, and that various methods of estimating blood flow should be utilized. Actually, a number of these studies have been initiated, and we must await with interest the information which we hope will be forthcoming.

THE COMBINATION OF SYMPATHECTOMY AND THIOCYANATES IN THE TREATMENT OF EXPERIMENTAL AND ESSENTIAL, OR HIGH DIASTOLIC, HYPERTENSION*

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AIDED BY THE GRUNOW SURGICAL FUND

IN 1938, Barker and Davis[1] formulated a plan for the study of patients with essential hypertension for whom surgical therapy might be undertaken. In 1939,[2] and again in 1948,[3] it was pointed out that sympathectomy alone had not been successful in permanently reducing the blood pressure levels of patients with the high diastolic type of hypertension, regardless of the extent of the operation. It was emphasized, however, that in this carefully chosen and specific group of patients sympathectomy had caused those who were resistant to thiocyanate therapy preoperatively to become sensitive to administration of the drug. Further, there were no significant changes in the blood pressure levels, or heart size, unless the patients were given thiocyanates postoperatively. We have attempted to find a physiologic explanation for the good clinical results produced by a combination of sympathectomy and the thiocyanates in the treatment of essential, or high diastolic, hypertension in man.

Pressor substances have been found in the blood of human beings with essential hypertension and in dogs with experimental renal hypertension. These pressor substances cannot be formed without participation of the liver and adrenal glands, and recent work[4-9] points to the adrenals as the main factor in the entire humoral mechanism involved. Sympathectomy depresses the function of the adrenal cortex and deprives the experimental animal of its ability to react completely to the stimuli of an emergency situation. Since the thiocyanates, combined with sympathectomy, gave better results in the treatment of hypertension in our group of patients than either method of treatment alone, in both human beings and animals, it was assumed that the thiocyanates produced a sustained depressor action by further inhibiting the function of the adrenal cortex. This would imply that the thiocyanates act upon the adrenal cortex, an hypothesis heretofore unconsidered.

EFFECT OF SUBCUTANEOUS INJECTIONS OF POTASSIUM THIOCYANATE ON THE ADRENAL CORTEX OF THE RAT

Anderson and Chen[10] stated that in rats oral administration of sodium, or potassium, thiocyanate in dosages of 100 to 200 mg. per kilo five days a week

* Read before the American Surgical Association, Colorado Springs, Colorado, April 19, 1950.

for 12 and eight weeks respectively caused no inhibition of their growth, as evidenced by their weight curve. The minimum lethal dosage ranged between 700 to 900 mg. per kilo. They reported data from the literature in which a dose of 1 Gm. per kilo of potassium thiocyanate injected subcutaneously was found to be lethal.

Nichols and Miller[11] studied the effects of sodium cyanide anoxia on the adrenal glands of the rat. They found that 2 mg. of sodium cyanide would kill a 150 Gm. rat in about 30 minutes. They injected rats subcutaneously with 1 mg. of sodium cyanide contained in 1 cc. of saline, followed by 0.5 mg. of sodium cyanide every hour for the following 20 hours. Other groups of rats were injected with 1 mg. of sodium cyanide followed by 0.5 mg. of the drug every half hour for the next 28 hours. The adrenal glands of the animals treated for 20 hours showed marked depletion of lipids in the inner cortical zones, fasciculata and reticularis, while the zona glomerulosa remained relatively unchanged. The animals treated for 28 hours showed the same changes in the adrenal cortex except to a more striking degree. In certain of these animals the lipids were depleted in the zona glomerulosa to almost the same extent as in the inner zones. These histologic changes are the same as those which occur in anoxic anoxia.

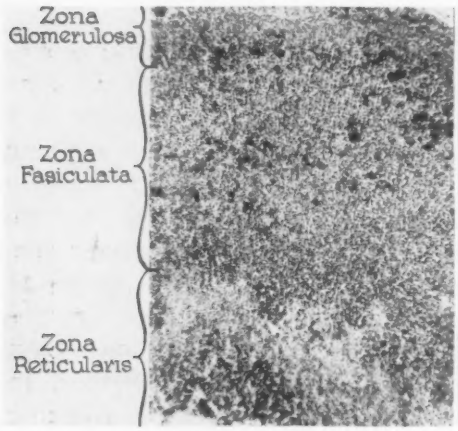
The SCN ion is the basis for the pharmacologic effects of the thiocyanate salts. The ion does not further dissociate in the body, since the atomic linkage is $-S-C\equiv N$, and it therefore has no action in common with cyanide. Indeed, Goodman and Gilman[12] have shown that the cyanides are detoxified in the body by conversion to the stable and much less toxic thiocyanate.

In view of the results of Nichols and Miller, it occurred to us that part of, if not all, the effect of cyanide anoxia on the adrenal cortex in the rat is due to the converted cyanide in the body, since rats received dosages far beyond the lethal dose without harm. Furthermore, the changes observed in the adrenal cortex by these workers are identical with those of anoxic anoxia and occur while the arterial oxygen tension is normal.

Five female white rats of 150 Gm. weight received subcutaneous injections of 1 mg. of potassium thiocyanate contained in saline every hour for eight hours the first and second day and 2 mg. every two hours the third day. Another group of five rats of the same weight received subcutaneous injections of the same drug in doses of 20 mg. every hour in a five-hour period. Before sacrificing the animals blood was drawn by heart punctures for thiocyanate level determinations. A control group was injected with 1 cc. of saline at the same intervals. Food and water were permitted without restriction. All of the rats were sacrificed and no particular symptoms were observed during the experiments. The animals treated for five hours (20 mg. every hour) had blood thiocyanate levels which ranged from 17.6 to 19.0 mg. per 100 cc. The adrenals were removed but not weighed, and placed in 10 per cent formalin solution for 24 hours. The surrounding fat was then carefully dissected away and the glands were washed for one hour in tap water. Frozen sections were cut at 15 microns and stained by Mallory's[13] technic for fat droplets, except

that the cut frozen sections were transferred to 1 per cent formalin and the staining time in the scarlet red solution was three minutes.

Histologically, the adrenals of the control animals were entirely normal (Fig. 1). In general, the cortex of the adrenal glands of the rats injected with doses of potassium thiocyanate showed depletion of lipids in the glomerulosa, inner fasciculata and reticularis layers when compared with the control specimens. The extent of depletion in the three layers varied in each gland, although no great difference was observed between the left and right glands.



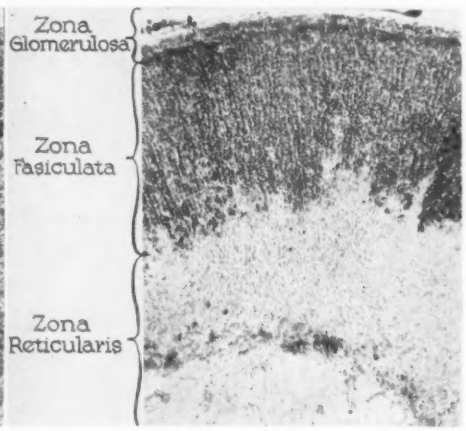


FIG. 1 FIG. 2

FIG. 1.—Photomicrograph of adrenal cortex or normal rat; sudan stain X 17. All of the layers contain lipids. The scarcity of sudanophilic material in the inner zona reticularis is a normal finding.

FIG 2.—Photomicrograph of adrenal cortex of a rat which received 100 mg. of potassium thiocyanate subcutaneously within a five hour period; sudan stain, X 17. Blood cyanate level at the time of sacrifice 19 mg. per 100 cc. The zona glomerulosa is reduced in size and depleted of lipids; the outer fasciculata and reticularis layers are also depleted of lipids. The intensity with which the lipid granules stain is less than in the control animals.

The glands of the animals which received 20 mg. every hour in a five-hour period showed a depleted and smaller glomerulosa layer and depletion of the inner fasciculata and reticularis zones (Fig. 2). The changes observed in the glomerulosa were more pronounced in the rats with the highest blood thiocyanate levels.

Sections of the livers of this group of rats were stained for fat in a similar manner. No particular pattern of fat distribution was observed in the control animals. In those rats which received 1 mg. of potassium thiocyanate the liver sections showed sudanophilic material accumulated around the central veins. The rats treated with 20 mg. doses of the drug showed no sudanophilic material at all, the liver trabeculae were edematous and the cells were vacuolated.

EFFECT OF THE ADMINISTRATION OF POTASSIUM AND SODIUM THIOCYANATE ON THE ADRENAL CORTEX OF DOGS

Dogs are more susceptible to thiocyanates than rats. According to Anderson and Chen[10] daily doses of either sodium or potassium thiocyanate equal to or exceeding 100 mg. per kilo produced, with few exceptions, rapid loss of weight, toxic symptoms and finally death. The toxic symptoms observed were apathy, head droop and ataxia. No uniform pathologic lesions could be made out to account for the animals' death. In dogs, a single dose of 100 mg. per kilo of either thiocyanate salt brings about a maximum blood concentration of 12 to 20 mg. per 100 cc. and the drug can be found in the blood stream for more than three days.

Lindberg, Wald, and Barker[14] showed that upon administration of sulphocyanates to normal dogs there was a prompt fall in the blood cholesterol value and a direct parallel existed between elevation of the blood thiocyanates and depression of the blood cholesterols. With "toxic" doses of the drug there was a proportionate suppression of both the albumin and globulin proteins. The fall in the erythrocyte count and the hematocrit in the blood of the dogs was striking and was explained by changes in the bone marrow. Marked fatty vacuolization of the parenchymal cells of the liver suggested functional hepatic changes reflected in the blood cholesterol and the total blood proteins. Anatomical changes in the adrenal glands were not found and chemical analysis of the blood with special reference to sugar, sodium, potassium and chloride metabolism failed to indicate any depression of the function of the adrenal gland.

It must be emphasized that the term "toxic doses" used by these workers means the doses of oral sulphocyanate salts necessary to bring the blood concentration of the drug above 12 mg. per 100 cc. For them, toxic concentrations are 15 to 20 mg. of the drug in the blood. Anderson and Chen[10] have stated that 1 Gm. per kilo of potassium thiocyanate intravenously is a lethal dose for dogs but 0.8 Gm. per kilo of the sodium salt is not lethal.

In view of the effect obtained upon the adrenal cortex of rats treated with subcutaneous injections of potassium thiocyanate, we studied the effect of different doses of potassium and sodium sulphocyanate on the adrenal cortex of normal dogs by different methods of administration. The dogs were closely observed during the course of the experiment and periodic determinations of the blood concentration of the drug were made. Other blood analyses were also performed, especially those which are considered to reflect adrenal cortex function. At different intervals the dogs were sacrificed, the adrenal glands removed and prepared for histologic sections in the manner described for rats.

The results obtained are shown in Table I. It can be seen that potassium thiocyanate by mouth produces gastro-intestinal symptoms which do not appear to be related to the concentration reached in the blood. Dog No. 3 had one ureter ligated before starting the experiment. The concentration reached in

TABLE I.—*The Combination of Sympathectomy and Thiocyanates in the Treatment of Experimental and Essential, or High Diastolic, Hypertension*

Dog No.	Weight Kg.	Salt of SCN	Method of Administration	Dose Mg./Kg.	Date	Blood SCN Mg./100 cc.	Hematocrit	Sediment Rate	B.U.N.	Glucose	Na % MEQ.	Na % MGAM.	K % MEQ.	K % MGM.	Comments
1	10.7	...	.....	.....	9–28										
Control					10–1	....	39.8								
					10–7	....	40.5								
2	8	K	Oral Daily	50	9–29										
					9–30										
					10–1	5.10	49.0	....	....	....	....	....	....	....	Dog alert—well
					10–2	....	....	....	....	....	....	....	....	....	Vomit
					10–3	11.80	42.7	....	....	....	....	....	....	....	Slight diarrhea
					10–4	....	....	....	....	....	....	....	....	....	Slight diarrhea
					10–5	15.30	39.0	....	....	....	....	....	....	....	Diarrhea increased—not eating
					10–6	....	....	....	....	....	....	....	....	....	Did not eat—diarrhea persisted
					10–7	16.40	37.5	....	....	....	....	....	....	....	Weight 8 Kg., sacrificed
3	6.3	K	Oral Daily	70 to 90	9–28	....	....	....	....	....	....	....	....	....	Right ureter ligated
					9–29	....	....	....	....	....	....	....	....	....	Active and alert
					9–30										
					10–1	8.75	42.0	....	....	....	....	....	....	....	Active
					10–2	....	....	....	....	....	....	....	....	....	Not taking food
					10–3	15.0	38.0	....	....	....	....	....	....	....	Not taking food
					10–4	....	....	....	....	....	....	....	....	....	Not taking food, diarrhea
					10–5	37.6	8.20	....	....	....	....	....	....	....	Not taking food, diarrhea
					10–6	....	....	....	....	....	....	....	....	....	Not taking food, diarrhea, tablets of SCN passed in the stool!
					10–7	36.5	18.2	....	....	....	....	....	....	....	Weight—5.9 Kg., sacrificed
															Intestinal petechiae—right kidney filled with purulent fluid
4	9	...	.....	.....	10–31										
Control					9:45 a.m.	....	47.0	1.0	17.5	....	143	330	4.5	17.5	
					11:30 a.m.	....	44.0	13.0	16.2	....	143	334.2	4.5	17.5	
					3:00 p.m.	....	44.0	15.0	16.0	....	145	334	4.5	17.5	
					4:10 p.m.	....	44.0	15.0	15.0	....	145	334	4.5	17.5	Sacrificed
5	9	Na	Intramuscular	3 Injections of 1.396 Gm. in 20 c.c. caline every 2 hours	10–31										
					9:45 a.m.	....	47.0	0.	22.0	....	143	330	4.5	17.5	Injection painful
					11:30 a.m.	23.2	45.0	0.3	20.3	....	145.5	334.2	4.5	17.5	Slight diarrhea
					3:00 p.m.	32.0	45.0	0.5	16.5	....	143	330	4.5	17.5	Depressed
					4:10 p.m.	84.0	44.0	0.7	18.0	....	143	330	4.5	17.5	Sacrificed, adrenals larger than control

TABLE I.—(*Continued*)

6	11.5	...	.....	.....	11–30	....	41	45	11.5	....	113.5	261.0	5.0	19.5	
Control					12–5	....	35	58	14.8	....	140	322.0	3.75	14.6	
					12–9	....	36	55	13.0	....	142.8	330.0	5.0	19.5	
					12–15	....	Hemolyzed	....	23.0	....	143.5	330.0	5.25	20.4	Sacrificed
7	12.7	Na	Intra-	100	11–30	....	56	0	11.0	....	150	345	4.5	17.5	
			venous	Daily	12–1	20.0	....	....	....	....	....	....	....	....	No signs
			daily	.....	12–2	29.3	....	....	....	....	....	....	....	....	No signs
					12–3	....	....	....	....	....	....	....	....	....	No signs
					12–5	17.1	52.0	11	22.5	....	137.5	316.0	3.75	14.8	Depressed—not eating
					12–6	19.45	44.5	....	....	....	....	....	....	....	Diarrhea—not eating
					12–7	29.89	42.5	....	....	....	....	....	....	....	Muscle rigidity, weight 9.5 Kg.
					12–8	39.8	48.7	....	....	....	....	....	....	....	Diarrhea persists
					12–9	50.86	....	....	18.0	....	135.0	310.0	3.0	11.7	Diarrhea persists
					12–10	....	....	....	....	....	....	....	....	....	Diarrhea persists
					12–12	58.96	47.5	....	46.5	....	118.5	272	2.0	7.8	Weight: 8.1 Kg. moribund—sacrificed
8	9.1	Na	Intra-	150	12–27	....	43.8								
			venous	Daily			43.3	7	20.25	....	147.8	340	5.0	19.5	B. P: 138
			daily		12–28	23.24	44.5	10	....	....	....	....	....	....	No symptoms
					12–29	38.52	45.5	12	19.5	....	147.8	340	6.0	25.4	Weight: 8.6 Kg. B. P: 108
9	12.7	Na	Intra-	100	1–4	....	41.0	7	26.9	....	150	346	5.25	20.5	B. P: 122
			venous	Daily	1–5	19.8	....	....	....	....	....	....	....	....	
			daily		1–6	31.7	44.5	14	....	....	....	....	....	....	Depressed, no other symptoms
					1–7	....	....	....	....	....	....	....	....	....	Depressed, no other symptoms
					1–9	17.8	39.0	41	11.0	....	137	316	3.75	14.6	Depressed, no other symptoms
					1–10	15.8	38.0	35	....	....	....	....	....	....	Depressed, no other symptoms
					1–11	29.5	35.1	49	12.5	....	....	....	....	....	Depressed, no other symptoms
					1–11										
					11:15 a.m.	52.44	38.0	51	18.0	....	143	329	3.40	13.3	B.P: 96 weight: 10.9 Kg.—sacrificed
10	9.1	Na	Intra-	150	1–10	....	43	1	19.8	....	141	324	4.25	16.6	B. P: 114
			venous	Daily	1–11	22.17	43.5	8	....	....	....	....	....	....	No symptoms
			daily		1–12	34.20	48	9	....	....	....	....	....	....	No symptoms
					1–13										
					9:30 a.m.	45.04	42	27	....	....	128.5	296	3.75	14.6	No symptoms, weight: 9.1 Kg.
					1–13										
					12:00	67.40	42	35	35.5	....	....	....	....	....	B. P.: 99—Extreme muscle rigidity, diarrhea
11	13.7	Na	Intra-	101	1–18	....	46	6	8.9	92	143.5	330	4.5	19.5	Anorexia
			venous	Daily	1–19	15.9	45	....	....	85	....	....	....	....	Slight diarrhea
			daily		1–20	22.8	48.7	0	....	86.5	....	....	....	....	Rigidity
					11:30 a.m.	46.5	47.8	4	12.5	87	142.8	329	3.5	13.6	Severe diarrhea

the blood was more than double that of Dog No. 2 and undoubtedly was due to the kidney exclusion. Symptoms, however, did not differ.

The intramuscular injection of sodium thiocyanate was painful, due to the hypertonicity of the solution (Sodium thiocyanate 1.396 Gm. in 20 cc., representing 5 per cent thiocyanate ion). However, the intravenous injection of this drug did not produce any immediate symptoms if the injection was given slowly. A high level of the drug was found in the blood one hour after the last injection of a series of three given every two-hour period. When sodium thiocyanate was given every 24 hours, the level in the blood varied but showed a progressive increase in the course of the experiment. The highest level was observed shortly after the injection was made (Dogs No. 10 and No. 11, Table I). The blood level varied widely in the dogs submitted to a single daily injection and did not bear any relationship to the dose used per kilogram of body weight. The intravenous route did not produce gastro-intestinal disturbances as did potassium thiocyanate when given by mouth.

In this series of experiments all the symptoms observed have already been described in the literature as toxic manifestations of thiocyanate. It must be emphasized, however, that no relationship could be found between the dose per kilogram or the level reached in the blood and the symptoms. Most of the animals lost weight, dehydration became marked and muscle rigidity was observed as the experimental period became prolonged. However, upon discontinuing the drug, symptoms would disappear and the dogs would recover.

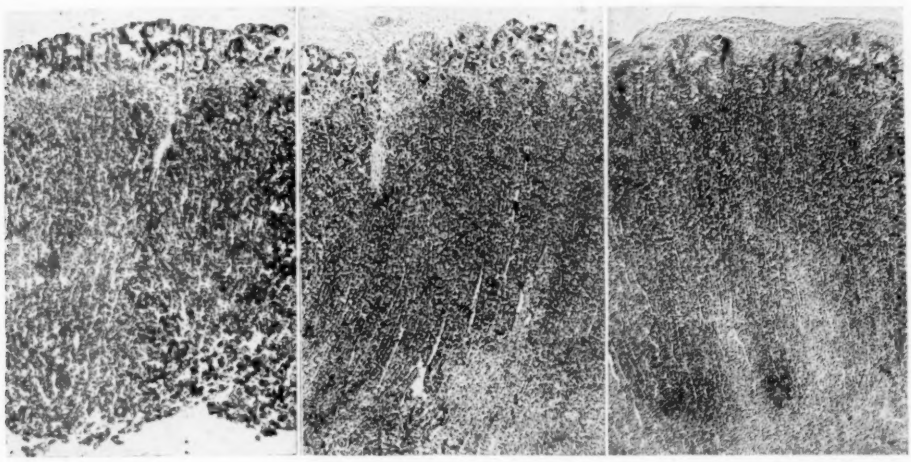
The changes found in the blood were also not related to the dose. Anemia and an accelerated sedimentation rate were common findings. Regardless of the anemia, increase of the hematocrit was frequently observed, indicating a profound alteration in the fluid balance. Dehydration and loss of weight accompanied the changes and were very marked when the blood sodium and potassium was low. Blood urea nitrogen increased occasionally and may be attributed to renal or adrenal insufficiency. The most conspicuous change found was the decrease in sodium and potassium. In only one dog of this series was a decrease in the blood sodium and an increase in blood potassium found.

The cortex of all of the adrenal glands showed a depletion of the lipid content in all layers. The depletion was more marked and uniform through all layers in the animals with the highest level of blood cyanate. No differences were observed when the right and left glands were compared. The depletion was seen to be very marked in the glomerulosa in the dogs with a decrease in the blood sodium and potassium (Fig. 3).

Nichols[15] presented analyses of adrenal glands of rats under various degrees of anoxia which indicated that there is a depletion of lipids in the inner zones of the cortex, while the glomerulosa zone is relatively resistant. Marked recovery of lipids occurs in five hours. Quantitative chemical analyses for the various fat fractions closely paralleled the histochemical observations. Nichols and Miller[11] also found that histotoxic anoxia induced by sodium cyanide

produces the same changes in the adrenal as does anoxic anoxia and that these changes can occur while the arterial blood is saturated with oxygen. Our results in rats injected with potassium thiocyanate in non-lethal doses parallel those of Nichols and Miller, although we have not carried out chemical analyses of the various fat fractions.

Thiocyanates may act on the adrenal cortex by producing histotoxic anoxia. It is known that cyanides are detoxified in the body by conversion to thio-



A B C

FIG. 3.—Photomicrographs of adrenal cortex of dogs; sudan stain X 37.

(a) Right adrenal cortex of 9 kg. control dog; all layers are filled with intensely staining sudanophilic, large granules.

(b) Left adrenal cortex of 9 kg. dog which received two intravenous injections of sodium thiocyanate (153 mg. per kg.) within a 48-hour period; blood cyanate level at the time of sacrifice 38.52 mg. per 100 cc. There is a depletion of the lipids in all layers, but it is more marked in the zona glomerulosa.

(c) Right adrenal cortex of 9.1 kg. dog which received one intravenous injection of sodium thiocyanate (150 mg. per kg.) every 24 hours for four injections; blood cyanate level at the time of sacrifice 67.40 mg. per 100 cc. There was a blood sodium and potassium decrease. There is a depletion of the lipids in all layers, and the staining intensity of the sudanophilic material, which has lost its granular appearance, is uniformly decreased.

cyanate and that the thiocyanate ion does not further dissociate in the body. Furthermore Friend and Robinson[16] showed that sodium thiocyanate depresses oxygen consumption of the liver cells in rats in doses between 20 and 30 mg. per 100 cc.

Weight by weight sodium thiocyanate contains more thiocyanate ions than potassium thiocyanate. Davis and Barker[17] found that cardiac fibrillation was the reaction of the heart to the potassium ion in the drug, with a resulting sharp rise in the blood pressure. When sodium thiocyanate was injected such an effect was not observed. Our results show that no immediate or acute symptoms are observed after the intravenous injection of large doses of sodium thiocyanate to dogs.

It has been stated that the cyanates are stored in the body where they are widely distributed in the body fluids and tissues and that their toxic action is cumulative. The rate of excretion from the body is extremely variable. From the work of Lindberg, Wald, and Barker[14] it appears that blood concentrations of 15 to 20 mg. will produce changes in the erythrocyte count, hematocrit values, total serum proteins, plasma cholesterol and sedimentation rate which becomes exaggerated as the blood level rises beyond these concentrations. According to these workers the blood changes only mirror other systemic alterations and the vasodilating effect of the drug occurs long before these changes take place.

With blood concentrations higher than those pointed out by them, and produced by the intravenous injection of sodium thiocyanate, we have observed the same responses in the blood but no generalized symptoms could be correlated with these levels. Gastro-intestinal disturbances rarely were observed when the drug was administered intravenously. Unless depression and apathy are ascribed to the anemia no other correlation seems warranted. Fluid imbalance and changes in mineral metabolism would explain better the most common symptoms found, i.e., weight loss, muscular rigidity, apathy and depression; and these may be related to sodium and potassium changes found in the blood.

The experimental results are shown in Table II. It can be seen that the level reached in the blood does not bear a close relationship with the symptoms nor the symptoms with the dose per kilogram. The changes in the elements of the blood studied are more conspicuous the more prolonged the experimental period. If a very high blood concentration is reached quickly symptoms do not occur. (Dog No. 7, Table II.) It may appear that symptoms are more evident when the drug has been distributed all through the body fluids and alteration of some organs has taken place.

Depletion of the lipid content found in the cortex of all the adrenal glands leads us to assume that some functions of the adrenal cortex may be altered by the presence of the drug in the circulation. The depletion and intensity with which the sudanophilic material stains parallel the concentration of the drug in the blood. Marked depletion has been observed without symptoms or blood chemistry changes with the highest blood concentration of thiocyanate.

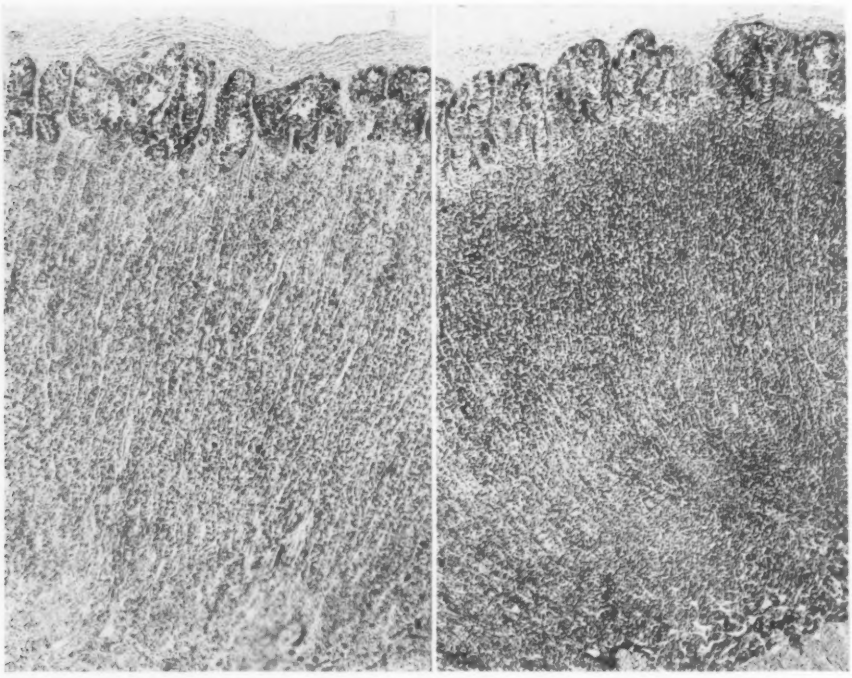
It appears, however, that the depletion of the glomerulosa layer when a high blood concentration of the drug is quickly obtained and the persistent, depleted glomerulosa when the changes in the blood elements are more acute have some relationship to the drug itself. If the changes in blood sodium and potassium are the cause or effect of the adrenal cortex alterations cannot be said at the present time.

Thiocyanate is considered a substance the toxicity of which can be measured by the determination of the blood concentration. Its main characteristic is that it accumulates in the body and remains in the circulation for a long period. Our finding that the adrenal cortex of the dog is affected when the

TABLE II.—*The Combination of Sympathectomy and Thiocyanates in the Treatment of Experimental and Essential, or High Diastolic, Hypertension*

Animal	Duration of Experiment		Drug, Amount and How Given	Dose per Kg.	Highest Concentration of SCN in Blood Mg/100/cc.	Changes Observed		Depletion of Fat Droplet Content of Adrenal Cortex
	Days	Hours				Symptoms	Blood	
Rat 1	2	2	Subcutaneous 20 Mg. KSCN	.013 Mg.	....	Painful reaction to injection	.....	Greater in glomerulosa than in outer fasciculata and reticularis
Rat 2	...	5	Subcutaneous 100 Mg. KSCN	.066 Mg.	19.0	Painful reaction to injection	.....	Greater in glomerulosa than in outer and greater than in inner fasciculata and reticularis
Dog 1	9	...	Oral 3.6 Gm. KSCN	450 Mg.	16.40	Vomiting, diarrhea, anorexia, loss of weight	Anemia	Intensity uniformly decreased. Greater in glomerulosa than in outer fasciculata and reticularis
Dog 2	9	...	Oral 3.6 Gm. KSCN	571 Mg.	36.5	Vomiting, diarrhea, anorexia, loss of weight	Anemia	Intensity uniformly decreased
Dog 3	2	...	Intravenous 2.792 Gm. NaSCN	306 Mg.	38.52	No symptoms, slight weight loss	Anemia, hemoconcentration, sedimentation rate accelerated. K increased	Intensity uniformly decreased
Dog 4	8	...	Intravenous 11.168 Gm. NaSCN	879 Mg.	52.44	Depression, weight loss	Anemia, sedimentation rate accelerated	Greater in glomerulosa than in inner and greater than in outer fasciculata and reticularis
Dog 5	11	...	Intravenous 15.356 Gm. NaSCN	1.2 Gm.	58.96	Anorexia, diarrhea, weight loss, muscle rigidity	Na decreased. K decreased. Anemia, hemoconcentration, sedimentation rate accelerated, uremia	Wider "clear zone". Intensity uniformly decreased. Greater in inner than in outer fasciculata and reticularis
Dog 6	3	...	Intravenous 4.188 Gm. NaSCN	305 Mg.	46.5	Anorexia, diarrhea, muscle rigidity	Na decreased. K decreased Hemoconcentration	Uniform depletion. Greater in other layers than in reticularis
Dog 7	4	...	Intravenous 5.584 Gm. NaSCN	558 Mg.	67.40	No symptoms	Na decreased. K decreased Anemia, sedimentation rate increased, uremia	Uniform depletion. Greater in glomerulosa than in other layers
Dog 8	...	5	Intramuscular 4.188 Gm. NaSCN	463 Mg.	84.0	Depression, diarrhea, painful reaction to injection	Na decreased K decreased Anemia, sedimentation rate increased	Greater in glomerulosa than outer fasciculata and reticularis

drug is injected intravenously allows us to assume that this experiment can be compared to one in which the dog is submitted to a prolonged stress. The fact is, however, that as long as the drug remains in the blood the histologic picture of a "resistance phase" in the adrenal cortex is not seen; i.e., lipids do not reaccumulate in the fasciculata layer. In fact, the appearance of the gland is similar to that seen in the "exhaustion phase."



A B

FIG. 4.—Photomicrographs of adrenal cortex of dogs; sudan stain X 54.

(a) Left adrenal cortex of 8.5 kg. dog which had the liver branches of the hepatic artery ligated. The dog died 24 hours later, with hypoglycemia. The size of the sudanophilic granules and the intensity of the stain in the zona filomerulosa are similar to control animals. All of the other layers are depleted of lipids.

(b) Left adrenal cortex of 7.8 kg. dog which received 85 units of alpha toxin of *Clostridium Welchii* per kilo intravenously by the drip method in 20 cc. of normal saline during one hour. The animal died three and one-half hours after the injection with a hypoglycemia. There is a uniform depletion of lipids in all layers.

To gain more information under the conditions of these experiments to show whether the absence of cortical lipids is an indication of activity or rest of the gland, we studied the adrenal glands of dogs dying after ligation of liver branches of the hepatic artery and after intravenous injection of the alpha toxin of clostridium Welchii. Both procedures are considered to produce toxic death,[18] accompanied by hypoglycemia (Fig. 4), and we have chosen to make a comparison because the appearance of the adrenal cortex is similar to that found in the dogs injected with thiocyanate, but in the latter

toxic deaths did not occur. Although the histologic pictures are similar except for more depletion of the lipids in the glomerulosa layer in the thiocyanate dogs, hypoglycemia was not found. This difference could be explained by considering that the dogs given thiocyanates were not in a moribund state as were those injected with the toxin when blood was drawn for chemical analysis; or, that hypoglycemia might not be the result of a depleted cortex, since the experiments used as a comparison may produce hypoglycemia through other mechanisms, for example, liver injury. On the other hand, changes related with carbohydrate metabolism in adrenal cortical hyperfunction have not yet been reported in the literature when stress is the cortical stimulant, according to Ingle.[19]

The symptoms and blood chemistry changes found in the thiocyanate dogs suggest that the function of the adrenal cortex is insufficient. Since similar histologic appearances of the gland have been observed when single large doses of the drug were injected, it is assumed that at least as long as the thiocyanate ion is in the body fluids the adrenal cortex is unable to re-accumulate lipids at a normal rate. Our esults substantiate the earlier hypothesis that stimulation of adrenal cortical activity causes an increase of lipids and reduction of activity produces a decrease in lipids. Work is in progress to gain more information concerned with this aspect of the problem, since it is claimed by Deane and McKibbin[21] that a complete parallelism does not exist between sudanophilia and the more specific ketosteroid reactions in rats.

The role of the adrenal cortex in the adaptation of the body to noxious agents is widely accepted.[22] Under these conditions the adrenals undergo morphologic and cytochemical modifications. It is accepted, however, that the glomerulosa invariably fails to take any great part in these modifications. Nichols and Miller[11] found that large doses of cyanide in rats produced a depletion in the glomerulosa to almost the same extent as in the inner zones. We found similar results using potassium thiocyanate in rats, and potassium and sodium thiocyanates in dogs, with sodium and potassium changes in the blood, and with symptoms such as depression, apathy, loss of weight and muscular rigidity.

Since the mechanism which normally stimulates and regulates the glomerulosa is unknown, our experimental results add some support to the hypothesis that the secretory activity of the glomerulosa may be regulated by the concentration of one or more of the electrolytes in the body fluids. Thiocyanates, then, may act by inhibiting the adrenal cortex, more specifically in the zone related with the steroids which regulates the concentration of electrolytes in the body fluids. The thiocyanate ion may produce these changes first, by direct action on the glomerulosa due to its vasodilating action. Arterioles enter the cortex from the capsule. The cells near the capsule are, therefore, more advantageously situated with respect to a fresh supply of oxygenated blood. Second, by acting on other capillary beds of the body the concentration of one or more of the electrolytes in the body fluids may be altered and these, in turn, will influence glomerulosa function. Third, by inhibiting the

FIG. 5

A B

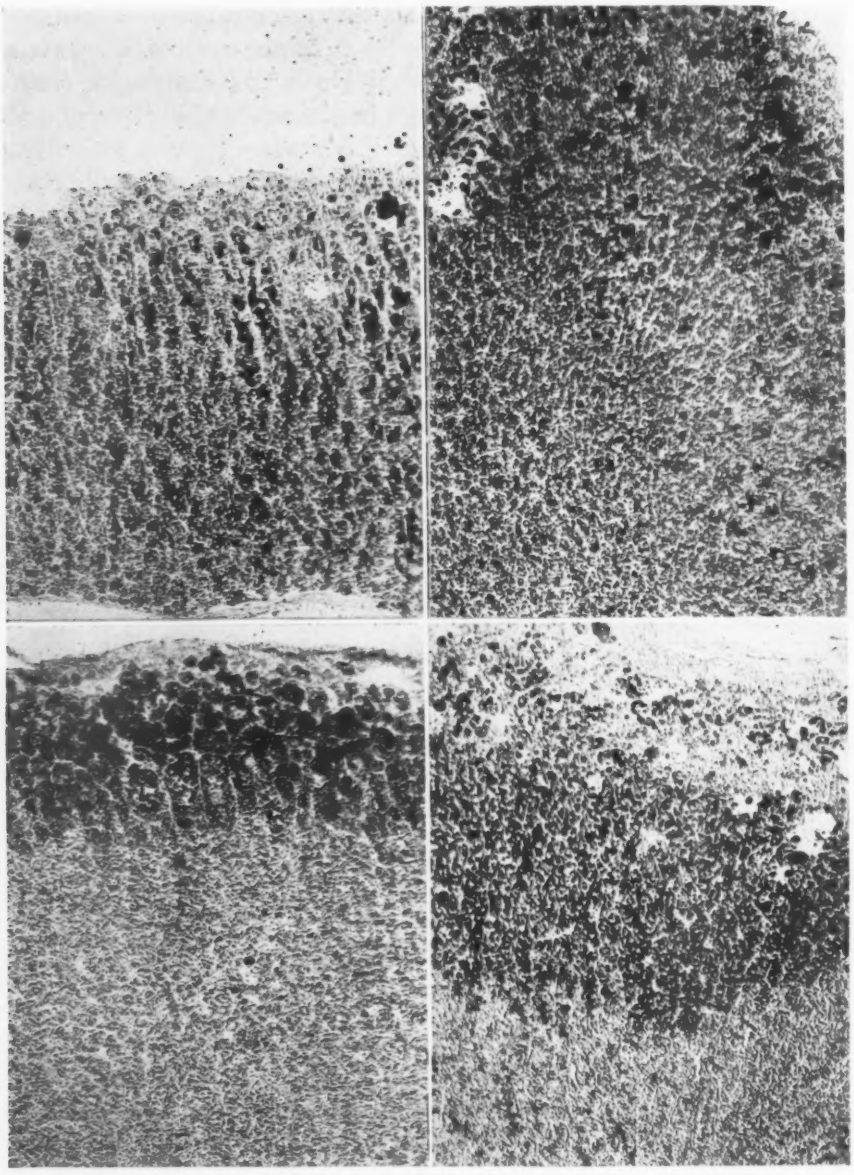


FIG. 6

A B

FIG. 5.—Photomicrograph of adrenal cortex of patient V. A., sudan stain X 50.
(a) Left adrenal cortex biopsy; blood thiocyanate level 15 mg. per 100 cc. The zona glomerulosa shows less lipids than normal; the fasciculata layer is loaded, and the zona reticularis contains a moderate amount.
(b) Right adrenal cortex biopsy; blood thiocyanate level zero. The zona glomerulosa shows more lipids than when thiocyanate is present in the blood; the

(*Continued on opposite page*)

capacity of the adrenal cortex to re-accumulate lipids, it is unable to cover the hormone demands of the body. All of the components of this hypothesis are to be investigated by further experimental work.

THE EFFECT OF THIOCYANATES UPON THE ADRENAL CORTEX OF HUMAN BEINGS

Histologic studies of the adrenal cortex of patients with essential, or high diastolic, hypertension upon whom bilateral thoraco-lumbar sympathectomy were being carried out were made when thiocyanate blood levels were high and at zero. One patient (V. A.) had been studied and treated for essential, high diastolic, hypertension for more than a year. Although tests had shown his blood pressure levels to be labile, he had not responded to well-controlled thiocyanate therapy, although his blood levels were increased to the point of gastro-intestinal intolerance for the drug. Therefore, he seemed to be a patient who fulfilled all of the requirements for sympathectomy in an effort to help him respond to thiocyanate therapy. He had begun to show some evidence of left cardiac failure and prior to operation his blood pressure readings were 220/120 to 280/160.

At the first operation, a left thoraco-lumbar sympathectomy was performed and a biopsy section was made of the left adrenal gland. At the time of this operation his blood thiocyanate level was 15 mg. per 100 cc. The zona glomerulosa of the adrenal cortex showed less lipids than normal; the fasciculata layer was loaded, and the zona reticularis contained a moderate amount. After this operation, thiocyanates were discontinued, and when the right thoraco-lumbar sympathectomy was performed his blood was completely free of the drug. Microscopic examination of the right adrenal cortex showed the zona glomerulosa to contain more lipids than normal; the fasciculata and reticularis layers showed less lipids than normal (Fig. 5).

A second patient, L. V., also had been treated for essential hypertension of the high diastolic type for over a year. He was extremely nervous, irritable, had suffered one attack of coronary occlusion and his blood pressure levels were consistently over 200 mm. systolic and 110 mm. diastolic in spite of periods of bed rest and intensive, well-controlled thiocyanate therapy with blood levels which could be elevated to 16 mg. per 100 cc. without symptoms of gastro-intestinal intolerance. Clinically he was sicker than the first patient, and had not responded to thiocyanate therapy in any way. All of the tests for blood pressure lability gave favorable responses and a left thoraco-

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fasciculata and reticularis layers show less lipids. The size of the sudanophilic granules is decreased as compared with the left adrenal cortex biopsy specimen.

FIG. 6.—Photomicrograph of adrenal cortex of patient L. V., sudan stain X 65.

(a) Left adrenal cortex biopsy; blood thiocyanate level zero. The zona glomerulosa is full of lipids; the outer layer of the zona fasciculata contains a normal amount, but the inner layer of this zone has less sudanophilic granules and the reticularis zone is depleted.

(b) Right adrenal cortex biopsy; blood thiocyanate level is 16 mg. per 100 cc. The glomerulosa and fasciculata zones contain less sudanophilic granules and the reticularis is depleted in some areas, though not significantly.

lumbar sympathectomy was performed after thiocyanates had been withdrawn and when his blood level was zero. Microscopic sections of the left adrenal gland showed the zona glomerulosa of the cortex to be full of lipids; the outer layer of the zona fasciculata contained about the normal amount but the inner layer of this zone showed less subanophilic granules and the reticularis was depleted of sudanophilic material. Sections of the right adrenal gland were made when the right thoraco-lumbar sympathectomy was performed and when the thiocyanate blood level had been raised to 16 mg. per 100 cc. The glomerulosa and fasciculata zones of the cortex contained a smaller amount of lipids and the reticularis was depleted in some areas though not significantly (Fig. 6).

The adrenal cortex of both of these patients showed changes in the distribution of the lipids within the different layers of blood thiocyanate levels which were as high as could be reached within the patient's gastro-intestinal tolerance. In each patient there was a different pattern of distribution of the lipids when the blood thiocyanate levels were zero and elevated. In both patients the microscopic pattern of the lipids in the adrenal cortical layers was similar to that found in our experiments with thiocyanates upon normal dogs.

In previous studies we have observed that certain patients with the high diastolic type of essential hypertension were resistant to the thiocyanates in that the doses necessary to lower their blood pressures and improve their symptoms had to be so great that the patients showed evidence of what has been termed "sulphocyanate intoxication." From these experiments upon animals we believe that it is not a question of toxicity of the drug but rather gastro-intestinal tolerance. It is well known that the amount of thiocyanate which can be given orally without vomiting and diarrhea varies greatly with each patient. In some, blood thiocyanate concentration cannot be elevated to effective levels by the oral administration of potassium thiocyanate. In others, blood levels heretofore considered high are not followed by improvement in symptoms. We have also pointed out that after sympathectomy in these patients, the doses of sulphocyanate necessary to maintain a blood level which is effective were much less; that is to say, the patient became more sensitive, or responded more favorably, to the drug. Our animal experiments have shown that gastro-intestinal intolerance develops from the oral administration of the thiocyanates, but when sodium thiocyanate is given intravenously, high blood level concentrations can be reached without the production of symptoms which have been considered to be due to thiocyanate toxicity.

The changes in the distribution of the lipid content in the three layers of the adrenal cortex in normal animals and in hypertensive patients thus far studied suggest to us that the thiocyanates have a particular affinity for action upon the adrenal cortex. The microscopic evidence of this action was observed in normal animals when potassium thiocyanate was administered orally but symptoms of gastro-intestinal intolerance were also produced. It could be argued that these adrenal cortical changes were due to the gastro-intestinal symptoms. However, the same changes were observed in the

adrenal cortex of normal animals when the thiocyanates were administered intravenously but gastro-intestinal symptoms did not occur. Therefore, we believe, that the intravenous administration of sodium thiocyanate in patients will avoid symptoms of gastro-intestinal intolerance, and will more effectively produce and maintain blood thiocyanate levels which will be reflected in lipid depletion in the adrenal cortex. We interpret the microscopic changes in the distribution of the lipid within the layers of the adrenal cortex as evidence that the thiocyanates act by inhibiting the function of the gland.

It is known that sympathectomy alone inhibits the function of the adrenal gland. However, we have pointed out that in patients with the high diastolic type of essential hypertension, sympathectomy alone does not affect the blood pressure levels or change the clinical course of the disease. We have also pointed out that after sympathectomy in these patients, the administration of thiocyanates alters the blood pressure levels and favorably affects the clinical course of the disease. Our experiments in normal animals and in human beings with the high diastolic type of essential hypertension show that the thiocyanates produce a change in the distribution and depletion of the lipids in the adrenal cortex. Therefore, we believe we may assume that the combination of sympathectomy and thiocyanate administration is more effective in inhibiting the function of the adrenal gland than either alone in the majority of this type of patients. That the adrenal gland is an important factor in essential hypertension is shown by the fact that adrenalectomy in animals with hypertension produced by the Goldblatt clamp is one of the two methods which lowers the blood pressure levels. The other method which is so effective in this type of experimental hypertension is the administration of thiocyanates.

To establish the microscopic pattern of depletion and distribution of lipids in the adrenal cortex in hypertensive patients it will be necessary (1) to study more biopsy specimens of the adrenal gland from patients with the high diastolic type of essential hypertension before and after sympathectomy with the blood free from thiocyanates and with high blood levels of the drug, and (2) to study the lipid depletion and distribution in the adrenal cortex of dogs with experimentally produced hypertension.

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RESTORATION OF FACIAL FUNCTION BY NERVE ANASTOMOSIS*

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The facial nerve is most commonly severed in the facial canal as a complicating factor in mastoid surgery. Undoubtedly, the best surgical treatment in this situation is an end-to-end suture or a nerve graft. This procedure is a highly technical one and there are only a few surgeons sufficiently skilled in mastoid surgery and nerve suture work to obtain consistently good results. On the other hand, hypoglossal facial anastomosis is such a relatively simple surgical procedure that a surgeon may expect a good result even though called upon to operate upon only an occasional case. Neuro-surgeons commonly carry out some form of facial nerve anastomosis following the total removal of an acoustic neuroma. In this operation the intracranial portion of the facial nerve is removed with the tumor and end-to-end suture is out of the question.

Recently Dr. Alexander and I have reviewed our acoustic neuroma material and this has given us an opportunity of assessing some long-term results of hypoglossal facial and spinal accessory facial anastomosis.

HYPOGLOSSAL FACIAL ANASTOMOSIS

Thirty-three patients were examined from three and one-half months to 15 years after a hypoglossal facial anastomosis performed by several different house officers and staff members. The average results should represent those to be expected from any group of surgeons using the usual end-to-end suture with a few fine interrupted silk sutures without tension at the suture line. The key to finding the facial nerve is a dissection which enables one to palpate the styloid process and visualize the posterior aspect of the parotid gland. The course of the nerve can then be imagined from the stylomastoid foramen to its entrance into the parotid gland. Working on this line the nerve will be found buried in dense fascia just as it enters the gland.

On the whole, we have been agreeably surprised by the excellent cosmetic results. At least 75 per cent had excellent restoration of resting facial symmetry. When talking or eating, there was considerable movement of the face, giving an animated facial appearance when most needed. A quiet smile could be managed with good symmetry; with a hearty laugh there was no movement of the paralyzed side of the face. In a few there was too much movement of the face when talking or eating. On the whole, however, the

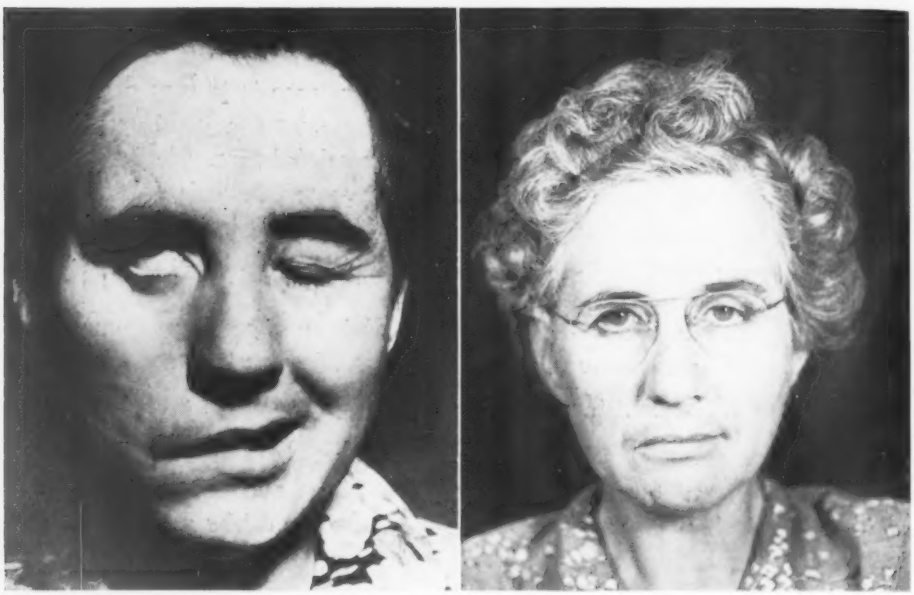
* Read before the American Surgical Association, Colorado Springs, Colorado, April 19, 1950.

patients and relatives were pleased with the results and we feel that we can endorse the simple surgical procedure of hypoglossal facial anastomosis.

Most patients were operated upon from two to six weeks after division of the facial nerve. It is of interest that one patient had the anastomosis performed two and a half years after section of the facial, and a good result was obtained.

SPINAL ACCESSORY FACIAL

We have seen three of our patients with a spinal accessory facial anastomosis. The cosmetic results were not nearly as good as the hypoglossal



A B

FIG. I.—Left: photo before hypoglossal-facial anastomosis. Right: 15 years after right hypoglossal-facial anastomosis. Face almost completely symmetrical at rest.

facial. At rest facial symmetry was often good, but the lack of facial animation when talking and eating was a detriment. Over-action and mass movement of the face accompanying any vigorous shrug of the shoulder was quite marked. Atrophy and droop of the shoulder was disfiguring and a few patients complained bitterly of pain and loss of function in the shoulder. One such patient, unable to do her usual heavy farm work, had function almost completely restored by Dr. Dewar and Dr. Harris of the Toronto General Hospital Orthopaedic Service. They are reporting the details of this operation in a separate preliminary report, which will be published at the same time as this paper.

Several other patients were examined who had had the spinal accessory nerve removed, together with the sternocleidomastoid muscle in radical neck dissections for cancer. In some of these the deformity was similar to that observed in our patients. In a few instances the innervation of the lower portion of the upper half of the trapezius muscle was intact, the scapula held back and up; in most of these cases the arm could be elevated in abduction almost normally. Since a portion of the trapezius muscle is supplied by branches from the third and fourth cervical nerves, it is likely that variation

FIG. 2

FIG. 3

FIG. 2.—Ten years after right hypoglossal-facial anastomosis. Movements of the face are symmetrical and patient presents a good cosmetic appearance at all times.

FIG. 3.—Three and one-half months after left hypoglossal facial anastomosis. At this early stage the anastomosis is functioning so that while smiling the face is only moderately distorted. The outer corners of the left lids have been sutured because of an insensitive cornea.

in the innervation of the trapezius explains the variation in the disability of patients in whom the spinal accessory nerve is cut. In those who have an innervation of a significant portion of the upper half of the trapezius by the cervical nerves, there is less disability than in individuals with innervation of the upper portion of the trapezius entirely by the spinal accessory nerve. The scapula must be held medially and upward to elevate the arm and apparently the levator scapulae and rhomboids, though hypertrophied, are not adequate to this task.

DESCENDENS HYPOGLOSSI NERVE SUTURED TO FACIAL NERVE AND THE DISTAL END OF THE HYPOGLOSSAL NERVE

Brief reference should be made to two patients in whom the descendens hypoglossi nerve was sutured to the distal end of the facial nerve. In the first patient this was done because the hypoglossal nerve had been damaged by the electro-surgical current. There was complete failure of return of any motion in the affected side of the face. In the second patient there was moderate disfiguring asymmetry of the face at rest and no motion on talking or moving the tongue. When the patient swallowed, however, the corner of the mouth on the side of the paralysis moved 1 to 2 cm. This movement was definite and consistent, but far from impressive.

Of the seven patients in whom the descendens hypoglossi was sutured to the distal stump of the hypoglossal, three have been examined. In two there was marked atrophy and asymmetry of the tongue, the innervation by the descendens hypoglossi being of no value in preventing atrophy. In one patient the paralyzed side of the tongue showed undulating movements and less atrophy than is ordinarily seen. Interestingly enough in one individual observed ten months after hypoglossal facial anastomosis, there was good function of the face and almost no atrophy of the side of the tongue on which the hypoglossal nerve had been sutured to the facial nerve; the tongue actually deviated slightly away from the affected side. The descendens hypoglossi was not anastomosed to the distal stump of the hypoglossal in this patient. Speech was not disturbed by paralysis of half of the tongue in any patient.

DISCUSSION

Neuro-surgeons in their practice are particularly concerned with patients who have had an intra-dural severance of the facial nerve. General surgeons can expect to be called upon to treat patients who have had the facial nerve injured in the neck or as a complication of mastoid surgery, particularly when it is not feasible to send the patient to a surgeon thoroughly trained in mastoid surgery and interested in the highly technical problem of nerve suture in the facial canal. Also, facial canal suture is not feasible or will fail in about 25 per cent of cases even in highly skilled hands. In all these situations, we believe hypoglossal facial anastomosis, and not spinal accessory facial anastomosis, to be the operation of choice. The use of fascia to restore symmetry of the face should be reserved for patients who have had a wide resection of the parotid gland with the facial nerve and its branches.

Dr. Claude Coleman has recently called our attention to the feasibility of obtaining a good result when the trunk of the facial nerve has been removed but not its main branches. He successfully anastomosed the split end of the spinal accessory to the three main trunks of the facial nerve. His patient has an excellent cosmetic result. Further experience with this operation may

prove that it is better to anastomose a nerve to the three main branches of the facial nerve than to its main trunk. If so, the relatively easy and reasonably satisfactory hypoglossal facial nerve trunk operation will be replaced by a much more time-consuming and difficult procedure.

DISCUSSION.—DR. GILBERT HORRAX: I think this excellent paper of Dr. McKenzie's has brought out most of the important points regarding restoration of function of the facial muscles after operation for acoustic tumors.

We feel, as he does, that the hypoglossal-facial rather than the spinal accessory-facial is the nearest approach to something ideal as we would like to have it.

None of these procedures, of course—as you realize—are at all like a real facial nerve. The ideal thing, of course, is to spare the facial nerve if you possibly can, in taking out an acoustic tumor. Unfortunately, that is rarely possible, because it is so bound up with the capsule of the tumor that the facial nerve is almost inevitably destroyed.

Dr. Olivecrona of Sweden has perfected a method by which I believe he is able to spare the facial in some 25 per cent of the patients, but whether he leaves some of the cells of the tumor or not, I am not entirely sure.

Certainly, most of these tumors start in the meatus, and it is difficult to see how the facial can be spared very frequently, when you have curetted out the meatus as we have to do.

We have saved the facial in perhaps half a dozen cases out of a hundred of acoustic neuromas, but that is a rare thing, and patients must be prepared for the facial paralysis. We always tell patients exactly what they are in for when they have an acoustic tumor.

As I say, I think nearly all neurosurgeons feel that the hypoglossal-facial anastomosis is the procedure of choice rather than the spinal accessory.

Whether this operation of Dr. Coleman's—which he reported last week—is going to be an addition to our armamentarium, so to speak, remains to be seen. Certainly, he had very good results in that case.

VENOUS SHUNTS IN BILATERAL PARASAGITTAL MENINGIOMA*

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ONE OF THE COMMON SITES for the growth of the usually benign tumor known as meningioma or meningeal fibroblastoma is the perasagittal region of the intracranial cavity. These tumors vary considerably in size and contour; however, most often they comprise a globoid firm mass attached to the undersurface of the dura mater adjacent to a lateral wall of the superior sagittal sinus. Although appearing to be unilateral, some of them have, nevertheless, grossly implicated the sinus. Others, bilaterally situated, have obliterated the lumen of this structure by compression and/or invasion. In any event, patients present themselves with symptoms and signs of a space-taking mass within the cranial cavity which is eventually shown to have occluded a segment of the superior sagittal sinus. In bilateral tumors, the growth is greater on one side, and when associated with hyperostosis, the cranial thickening is seldom equal in extent on either side of the midline. The findings as disclosed at operation indicate that the normal avenues for venous drainage have been encroached upon by the growth, thereby diverting the blood through collaterals or acquired venous shunts. As would be expected, gradual occlusion of the superior sagittal sinus by a meningioma would establish pathophysiologic conditions as regard blood flow that permit the surgeon to perform a block resection of the tumor and the obliterated sinus without permanent dysfunction of the cerebrum. In fact, it has been quite generally accepted that surgical resection of the superior sagittal sinus in the human may be performed without fear of producing irreversible alterations in brain function, provided the lumen of the sinus has already been completely obstructed by tumor.

Total removal of a bilateral meningioma that implicates the superior sagittal sinus in any manner cannot be accomplished except by incorporating the involved segment of the sinus in the resection. On the other hand, many neurosurgeons have reconciled themselves with sub-total removal of a unilateral parasagittal tumor, leaving in situ that part within the sinus. We have at times shared this timidity of practice, knowing full well that resection of a partially patent and functioning sinus, except for its rostral one-fourth, is frequently followed by grave cerebral alterations. In examples of bilateral tumor with the sinus occluded anterior to the site of union of the rolandic veins with the sinus, block resection of the tumor and the occluded segment of sinus may be carried out without fatality. In our series of 11 cases of bilateral meningiomas there were eight with the tumor situated anterior to the rolandic

* Read before the American Surgical Association, Colorado Springs, Colorado, April 19, 1950.

veno-sinus junction. There were no deaths; however, two of the eight had postoperative complications of a largely reversible character. Of the remaining three patients of the series of 11, two had tumors implicating the sinus at the rolandic veno-sinus junction. The superior sagittal sinus was obstructed in both of these, and following operation there was quadriplegia. One died on the third day after operation, while the other survived for three months. The remaining patient of the series is of special interest and the experience is herein presented in full. The story amply illustrates the importance of collaterals when a large portion of an occluded posterior half of the superior sagittal sinus is surgically resected.

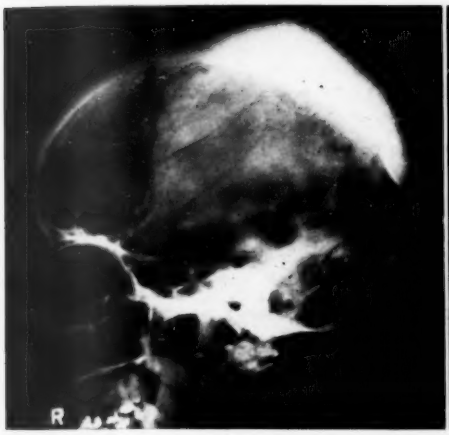

FIG. 1

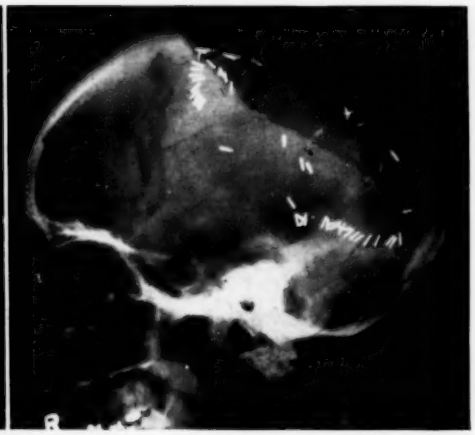

FIG. 2

FIG. 1.—Hyperostosis and prominent blood vessel channels of the skull.
FIG. 2.—Roentgenogram after third operation. Anterior rows of clips indicates site of division of falx rostrally, and posterior row the line of section just above straight sinus.

REPORT OF CASE

Lump on the posterior part of head for two years. Headache for one year. No other complaints. Bilateral papilledema. Obvious large, non-tender cranial hyperostosis. Operation in three stages: (a) excision of hyperostosis; (b) excision of tumor on right side, at which time it became necessary to excise the right occipital lobe; (c) removal of superior sagittal sinus, falx and attached tumor on left side. Cranioplasty.

T. A., a 20-year-old female, was admitted to the Brooklyn Hospital on March 21, 1949, complaining of intermittent headache which had never incapacitated her. Two years prior to admission her mother had noticed a painless, non-tender lump in the midline of the superior parietal region. At this time the prominence was estimated to be about half the size of one's palm. During the ensuing 2 years the mass slowly became more prominent until it reached the proportions shown in Figure 1. The patient continued with her work as a typist and had no complaints. Infrequent bi-temporal headache was first present about one year before entry, and it was for relief of this that she sought counsel of the family doctor. There had been no visual disturbance, nor any features suggesting intellectual impairment.

The patient was 5 feet 1 inch in height and weighed 122 pounds. She was alert, well-oriented and fully cooperative. There was no speech defect. One could palpate a large, firm, non-tender mass occupying the crown of the head, slightly greater to the right than the left of the midline. No bruit could be heard over any part of the head. After the hair had been removed, moderately prominent vessels of the scalp were visible. The pupils were normal. The optic discs were moderately choked bilaterally but no retinal hemorrhages were observed. No other abnormalities were disclosed, except possibly slight increase in the activity of the tendon reflexes in both the right upper and lower extremities.

The roentgen-ray examination showed the hyperostosis and blood vessel markings of the cranium as disclosed in Figure 1.

On March 23, 1949, under endotracheal anesthesia the cranial prominence was exposed through a highly vascular scalp. The strikingly prominent blood vessels (for the most part carrying venous blood of the periosteum) formed an interesting mosaic. During a three and a half hour procedure the exceedingly vascular, ivory-like hyperostosis was widely removed (Fig. 2). The dura was only moderately tense. At either end of the exposed superior sagittal sinus was a vein about half the size of a pencil, that led from the sinus into the diploe of what was considered to be normal bone. The posteriorly situated vein was readily occluded by pressure applied over a patty of Gel-foam, but bleeding from the rostral one was more difficult to control because of excessive intrasinus pressure. The dura was not opened.

The postoperative course was characterized by drowsiness. When aroused she complained of throbbing headache. Except for these, no abnormal features were present. The drowsy state and complaint of intermittent throbbing headache subsided on the fourth day. The choked discs remained unaltered.

On April 4, 1949 (12 days after the first operation), the scalp wound was re-opened. The dura was estimated to be more tense than at the conclusion of the first operation. It was incised on the right and reflected medially, disclosing a meningioma broadly attached to the falx, superior sagittal sinus, and under aspect of the surface dura. The moderately distended veins occupying the region of the central cerebral sulcus and also those leading off the occipital lobe passed directly through the tumor to join what was considered to be an occluded superior sagittal sinus. Division of these veins was begun at the rostral end of the tumor and completed just short of the occipital pole of the brain. Thereupon the tumor was dissected from the falx and right wall of the superior sagittal sinus. So far as could be determined, the sinus was not carrying any blood. Bleeding points of the falx were controlled by electro-coagulation. At the completion of this phase of the operation the brain did not appear unusually full, however, the cortical veins were very full but could be readily collapsed by slight pressure. Approximately 30 minutes following the ligation of the cerebral veins as described, the parietal region of the right cerebral hemisphere began to swell and rapidly reached such proportions that it spontaneously ruptured along its shoulder and discharged a sizable fresh blood clot. Bleeding of moderate amount through the spontaneous rent in the cortex continued, as did the protrusion of the entire area of brain exposed. In consideration of the situation, it was thought advisable to amputate the right occipital lobe. This was performed with dispatch, following which the herniated part of the brain gradually settled into the intracranial cavity. The cortical veins remained full. After hemostasis, the wound was closed.

Upon recovering from anesthesia the patient was alert, named nurses and doctors correctly, and could move the left shoulder and left arm. Left homonomous hemanopsia was evident. The face was symmetrical. The extremities of the right side were normal. There was no observable movement of the left forearm, hand and left lower extremity. Babinski's sign was present on the left side and equivocally so on the right. Tendon reflexes of the left upper extremity were slightly more brisk than the corresponding ones on the right side. Abdominal reflexes were not present. Tendon reflexes of the left lower extremity were less active than those on the right. Pinprick was appreciated

as painful throughout except for several irregular areas of the left leg and foot where this stimulus was reported to be less sharp. Two-point discrimination in the left hand was grossly impaired. Finger movements of the left hand returned on the sixth postoperative day (April tenth). Two-point discrimination and tactile sensibility were still grossly impaired in the left hand at this time. By the eighth postoperative day, movements in the left thigh and leg were observed, but no movements of the left foot or toes were present. Easily demonstrable impairment in appreciation of touch, two-point discrimination and toe motion in the extremities of the left side persisted. Three weeks after the second operation the patient was able to take a few steps with support. Also, progressive improvement in the use of the left hand was recorded.

On May 11, 1949 (37 days after the second operation), the scalp wound was reopened. The superior cerebral veins on the right side were normal in appearance. Incision of the dura on the left was carried out as it had been on the right side at the second operation. Upon reflecting the dura medially the tumor on this side was brought into view. The situation was about the same as that disclosed on the right side except that the tumor was slightly smaller. Beginning rostrally, all the exposed crossing veins involved in the tumor were divided. Thereupon the superior sinus, falx and inferior sagittal sinus were divided anteriorly, as indicated by the anterior row of clips in Figure 2, and then posteriorly just short of the straight sinus as shown by the posterior line of clips in this figure. The closure of the superior sinus was secured by sutures both rostrally and at the torcular Herophili. After observing the brain for 30 minutes, there was no evidence of swelling, nor did the ligated superior cerebral veins on the left side become distended. Plastic repair of the cranial defect was carried out and the wound closed.

Eight hours after this operation the patient was alert, well oriented and speech was intact. The face was symmetrical. No weakness of the right upper extremity and no change in the paretic state of the left upper extremity was observed. The right lower extremity, however, was markedly paretic, there being only slight motion of the right thigh. The paretic state of the left lower extremity was thought to be slightly greater than before the third operation. Babinski's sign was present bilaterally. Passive toe motion could not be identified by the patient on either side. These abnormal findings remained approximately the same for 3 days. During the ensuing 2 weeks there was progressive improvement in every respect. Motor power and the proprioceptive sensibilities in the right lower extremity returned first. There was steady improvement in the function of the extremities of the left side to the extent that the left hand was used in purposeful acts and she could walk with support. When discharged on May 27, 1949, the scalp wound was well healed and the contour of the head was as shown in Figure 3. The left homonomous hemanopsia remained complete.

The patient returned periodically for re-examination. Nine months after operation the left visual field defect was the same. The face was symmetrical. The left lower extremity was slightly circumducted when walking. There was definite but mild spasticity of this extremity. She had been dancing without difficulty. Ankle clonus was demonstrable bilaterally; however, Babinski's sign was not present. Toe and ankle motions were considered normal on the right but slightly impaired on the left side. Two-point discrimination and tactile sensation were as good in the left as in the right hand. Social activities had been resumed, although she had not returned to her former occupation as a typist.

Histologically, the sinusoids of the hyperostosed bone were occupied by tumor. The tumor from both the right and left side of the falx was a fibroblastic meningioma. The superior sagittal sinus was completely filled by tumor which extended from a point one centimeter distal to the site of surgical division rostrally to a point approximately one centimeter short of the torcular. Throughout the tumor tissue encased in the sinus were seen microscopic spaces that appeared to have been blood-carrying channels.

Comment. Wide removal of the cranium interrupted the main venous emissary that was serving as an outlet for blood of the patent superior sagittal sinus lying rostral to the segment occluded by tumor growth. This seemingly resulted in sufficient venous stasis in the brain to produce a drowsy state that persisted for four days. At the second operation it was thought that the superior cerebral veins of the right side were obstructed as they entered the tumor. It was obvious that the sinus was occluded by new growth. The veins were still functioning, as evidenced by the sequence of events that followed their ligation. It became apparent that the current of venous blood was in a normal direction, namely toward the sinus.

An additional maneuver was carried out at the second operation that probably influenced the findings at the third operation. After removing the tumor of the right side from the falx, bleeding points were controlled with coagulation. These were so numerous that the entire width of the falx was actually coagulated and no doubt the venous channels of this structure were occluded. This probably brought about an increase in the collaterals of the superior cerebral veins of the left brain. In all events, no calamitous sequelae followed the surgical division of the cerebral veins of the left side as occurred on the right.

In retrospect, the patient might have fared better if only half of the crossing veins had been ligated at the second operation.

DISCUSSION

Exclusive of the series reported by Olivecrona[1] of parasagittal meningiomas implicating the superior sagittal sinus for which block resection of a segment of the sinus was performed, we have been able to collect 33 cases from the literature: Küster,[2] one case; Kenyon,[3] one case; Rand,[4] one case; Cushing,[5] four cases (first in 1925); Towne,[6] one case; Grant,[7] one case; Vincent,[8] one case; Horrax,[9] two cases; Tönnis,[10] two cases; Davidoff,[11] one case; Adson and DaCosta,[12] two cases; Rowe,[13] one case; Dandy,[14] four cases; Jaeger,[15] ten cases; Love and Gay,[16] one case.

In 17 of this group of 33 patients, the segment of sinus removed was from its rostral third. It is difficult to make accurate estimates of the exact limits of the segment of sinus resected in the remaining 16 cases. It would seem from the data available that eight of these resections were performed in the mid-third and eight in the posterior third of the sinus. In Olivecrona's series of parasagittal meningiomas, there were 53 cases of block resection of the superior sagittal sinus. In 38 of these the sinus was considered to be completely occluded by the tumor and in the remaining 15 cases the tumor had incompletely obliterated it. The locations of the segment of sinus resected were not recorded in this communication.

Historically it seems desirable to briefly restate the case of sagittal sinus resection recorded by Küster in 1881, antedating the famous case of Godlee[17] by four years. Küster's patient had a midline frontal tumor said to be a "fibro-myxo-chondro-osteo-glio-sarcoma." Two operations were carried out.

At the first operation, that portion of tumor lying extradurally was for the most part removed. At a second operation (two months later) the flap of scalp was re-elevated and during the removal of the tumor the "sinus falciformis superior" was opened and clamped. Following this the sinus was divided at a level slightly above the middle of the forehead. From the description in the report it would seem that the major concern was prevention of air entering the sinus. The patient died about two months after the second operation from continued growth of the tumor.

To Olivecrona belongs the major credit for developing the radical operation of block resection of the superior sagittal sinus for the cure of meningiomas implicating this structure. Notable contributions to the subject have been made by both Dandy and Jaeger. In most of the papers reviewed, emphasis has been placed on the exact number of centimeters of sinus removed, the site of the resected part and whether or not the sinus was patent. Only Jaeger discussed the anatomical variations in the number and position of the superior cerebral veins in relation to the tumor. Although anatomical studies concerning the relationship of the cerebral veins to the superior sagittal sinus have been recorded by many anatomists, surgeons by and large have apparently not applied this anatomical knowledge. Casual mention has been made by a few surgeons regarding the "collaterals" that develop during and after closure of the sinus by tumor. As previously stated, we are here primarily concerned with the potential avenues of venous drainage in examples of occlusion of the sinus by tumor as well as what manner of venous shunts may become established after surgical resection of a part of an open sinus and/or ligation of superior cerebral veins. From observations made at operation we are of the opinion that during and after occlusion of the sinus by tumor, venous collaterals are spontaneously formed to carry the blood from both the highly vascular tumor and from the segment of sinus rostral to the site of occlusion.

In a series of 44 experiments carried out on fresh autopsy specimens with the dural envelope and major sinuses intact, save for the cavernous and a part of the petrosal system, we have been unable to fill the superior cerebral veins by injecting a contrast medium (under a pressure of less than 100 mm. Hg.) into the superior sagittal sinus with the sinus ligated just rostral to the torcular. In eight instances when extreme intrasinus pressure (600 mm. Hg.) was used, partial filling of cortical veins was accomplished. Using normal salt solution as well as fluid blood instead of the slightly heavier radiopaque medium, comparable results were obtained. Similar injections through a burr hole over the sinus with the skull otherwise intact filled only the large dural sinuses. Using a mixture of heparinized blood and red lead as contrast medium, injections into the closed sinus under extreme pressure (500 to 600 mm. Hg.) filled numerous small diploic channels as subsequently demonstrated roentgenographically (Fig. 4). From these observations in the normal human brain we have therefore drawn the conclusion that there is a valve-like action at the junction of the superior cerebral veins and the superior sagittal

sinus that largely prevents fluid entering the cerebral veins from the sinus. The obliquity at which the veins join the sinus lends support to the concept that during life there is a valve-like action that prevents reflux of blood from the sinus into the cortical veins. It seems possible that gradual occlusion of the sinus as obtains in tumor may be followed by some reversal of venous flow into the superior cerebral veins. The deduction that we have drawn from the injections of the fresh cadaver specimens as described and the observations made at operation does not support this hypothesis. It is reasonable to assume that the increased tension in the patent portion of sinus rostral to the obstruction is reflected in the superior cerebral veins and thereby may favor establish-

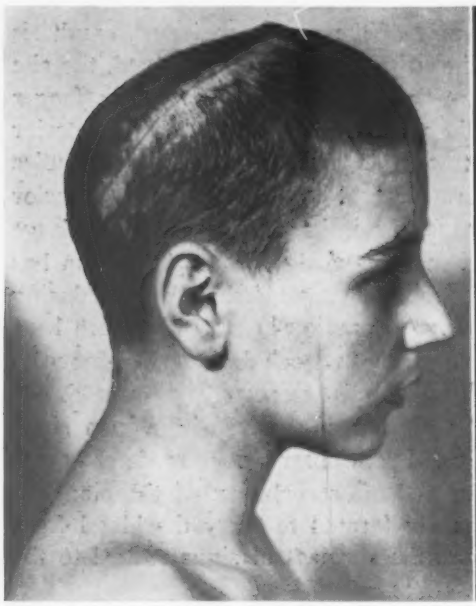

FIG. 3 FIG. 4

FIG. 3.—Contour of the head following cranioplasty.
FIG. 4.—Roentgenogram of the calvarium of a cadaver showing contrast medium in diploe following its injection into a "closed" superior sagittal sinus.

ment of collaterals between cortical venous channels. It is our opinion, however, that the major portion of the blood in the sinus anterior to the obstruction makes its exit from the intracranial cavity through enlarged emissaries to diploe and scalp.

Injections of various media (air, salt solution, heparinized blood and radiopaque mixture) into cerebral veins just short of the superior sagittal sinus demonstrated a relatively free anastomosis between all the cortical cerebral veins. Using air as a medium, all the veins of the lateral surface of a cerebral hemisphere could be instantly inflated. Using more viscid media, anastomosis could be demonstrated between the superior cerebral veins at the anterior frontal region and the spheno-parietal sinus (Fig. 5), between the

rolandic and sylvian groups (Fig. 6), and between the posterior and rolandic groups of veins (Fig 7). Moreover, injections of the great vein of Galen demonstrated extensive anastomosis of the internal venous system with the superficial veins (Fig. 8). These experiences serve to support the well-known fact that there are numerous connections between the veins of the brain. It

FIG. 5 FIG. 6

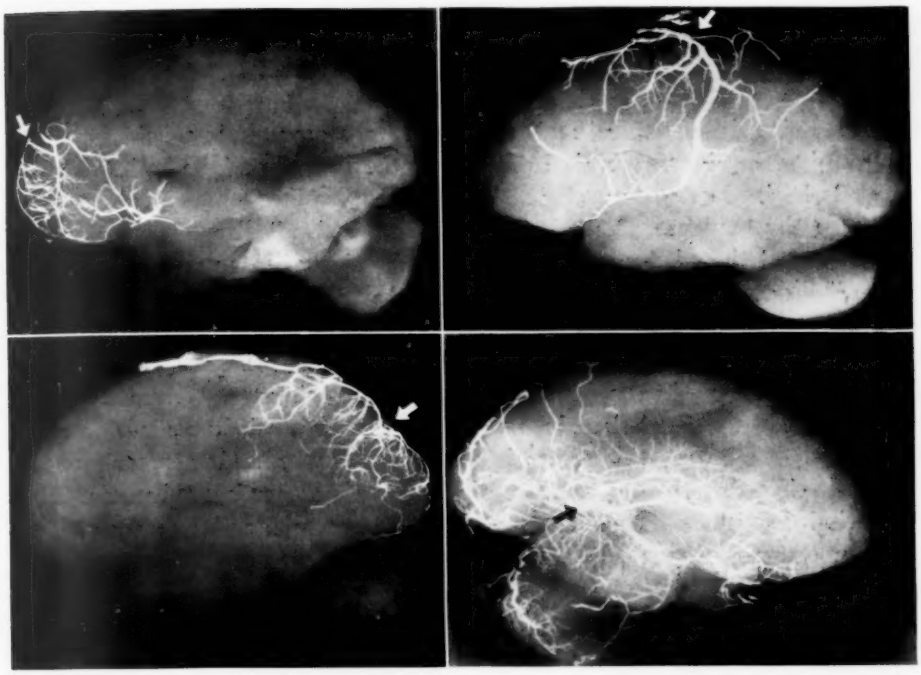

FIG. 7 FIG. 8

FIG. 5.—Demonstrating the anastomosis between the anterior group of the superior cerebral and sylvian veins. The connection to the spheno-parietal sinus is shown. Arrow indicates site of injection.

FIG. 6.—Injection of contrast medium at site indicated by arrow shows filling of the great anastomotic vein of Trolard.

FIG. 7.—Injection of contrast medium at site indicated by arrow demonstrates filling of regional veins and a part of the superior sagittal sinus.

FIG. 8.—Injection of contrast medium into the great vein of Galen (arrow) showing extensive connections of this system with the superficial veins.

seems unlikely, however, that these connections are sufficiently large to accommodate the volume of blood that would be shunted to them by sudden occlusion of more than one of the four major groups of cerebral veins that join the superior sinus. Furthermore, in consideration of the reflux protective mechanism at the veno-sinus junctions, it becomes obvious that sudden occlusion of an open superior sagittal sinus, certainly anywhere along its posterior half, is likely to be followed by serious consequences.

As has been reported, any occluded segment of sinus may be resected without subsequent complications; however, we would add, provided the sinus is completely obliterated and that only the obliterated portion is removed without damage to functioning veins. Therefore, one must give consideration to the manner in which the cerebral veins join the sinus or its lateral lacunae. In the anterior part of the sinus, the veins for the most part approach and unite with the sinus at a 90 degree angle. As one proceeds posteriorly the veins approach the sinus at a more acute angle in a rostrally directed manner. In fact, those just anterior to the rolandic point and those posterior to this area often parallel the sinus between the parietal and visceral dura for as much as two to three cm. before opening into the sinus or less often into a lateral lacuna. It is this anatomical reality that must receive utmost consideration in determining the site for surgical division of the sinus lest functioning venous channels be inadvertently occluded.

From the evidence available, namely that derived from observations at operation and that deduced from our anatomical studies as well as those of others,[18-21] one may say that progressive occlusion of a superior sagittal sinus by a bilateral meningioma results in the establishment of avenues of escape of venous blood through the falx cerebri, inferior sagittal sinus, the tumor, the dural veins, the emissary veins of the superior sinus and dura into the cranium and scalp and by partial reversal of the stream in the superior cerebral veins. We believe this reversal of flow occurs within the cerebral venous system itself rather than as a reflux of blood from the patent sinus rostral to the occluded segment. Of the above enumerated potential collaterals or shunts, the important ones are: (a) the emissaries connecting the superior sagittal sinus with the diploe and scalp and (b) the collaterals established in the cerebral veins. The total removal of a bilateral parasagittal meningioma of necessity requires the anatomical interruption of a major portion of the established collaterals except those of the cerebral venous system. Block resection at a single operation of an occluded segment of superior sagittal sinus situated anterior to the junction of the rolandic veins and the sinus may be performed without fatality but not always without alterations referable to the functions of the frontal lobes. In our experience, this cannot be said of the tumors that occlude the sinus at the rolandic area and/or posterior thereto. When there is minimal or no hyperostosis and the tumor occluding the sinus is so situated that it and the implicated sinus may be totally resected without division of functioning cerebral veins, a favorable outcome can be expected. Unfortunately, this patho-anatomical situation is rarely encountered. During a radical removal of a hyperostosed area, the emissary veins draining the segment of sinus rostral to the occlusion are divided. If the tumor has involved the veins at the rolandic point or posterior thereto, one should content himself with this as the primary procedure of a multiple-stage operation. At a second stage the tumor on one side of the falx should be removed, or if circumstances are as described in the case herein recorded, then one should divide only half of the cortical veins joining the implicated segment of sinus on one side. Thereafter,

further operations should be carried out, always having as a guide establishment of collaterals in advance of surgical sectioning of functioning venous channels.

CONCLUSION

From clinical experience with patients having bilateral parasagittal meningiomas and anatomical studies of the venous systems of the intracranial cavity, it has been shown that following gradual occlusion of the superior sagittal sinus by tumor, pre-existing venous channels may become enlarged in order to accommodate the blood shunted through them. The important collaterals or shunts are: (a) the emissaries connecting the superior sagittal sinus with the diploe and scalp and (b) the collaterals established in the superior cerebral venous system.

In the total removal of bilateral parasagittal meningioma of the posterior half of the head by block resection of the tumor and the obliterated sinus incorporated in it, one must give consideration to the number and size of emissary channels divided during the removal of the cranium. If the emissaries are large and/or numerous, removal of the bone should be considered the first stage of the total procedure. In addition, particular attention is to be given to the direction of blood flow in the superior cerebral veins that may be involved in the new growth.

Therefore we suggest that the operation for a lesion of the type under consideration (bilateral parasagittal meningioma obstructing a segment of the posterior half of the superior sagittal sinus) be a multiple-stage procedure.

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Discussion.—Dr. Bronson S. Ray: Dr. Browder voices the concern of all neurosurgeons faced with the possibility of having to tamper with the superior sagittal sinus. It is believed that the resection of any portion of the sagittal sinus behind the level of the central sulcus is never tolerated. The fact that sinus—which has been gradually removed and completely occluded by a tumor—can be removed without disaster is evidence that collateral circulation can develop.

There is considerable advantage if the presence of sinus occlusion and the degree of development of collateral circulation can be determined before the operation. To this end, we have developed a method of visualizing the intracranial venous system, and it is my thought that by showing our results in two cases, I can lend support to Dr. Browder's beliefs.

The method consists of injecting 35 per cent Diodrast through a catheter introduced into the anterior end of the superior sagittal sinus. Roentgenograms show that normally the contrast medium rapidly passes backward into the transverse sinuses and internal jugular veins. Normally the medium does not enter the cerebral or diploic veins even when the jugular veins are compressed.

A different pattern of the venous system is seen when a meningioma occludes the sagittal sinus. The contrast material passes back along the sagittal sinus to the point of obstruction and numerous cerebral, diploic and scalp veins constituting the collateral circulation are clearly visualized. Some of the material may get back into the posterior portion of the sagittal sinus via a circuitous route through cerebral veins.

The presence of adequate collateral venous circulation thus demonstrated by venography indicates the safety of resecting the superior sagittal sinus when invaded by tumor. But it is obvious that care must be given to the preservation of the collateral veins in the process of removing the tumor.

Dr. Browder's suggestion of performing the operation in stages is important, since the unavoidable interruption of any collateral veins allows for the redevelopment of collaterals between stages.

A STUDY OF THE VIABILITY OF AUTOGENOUS FROZEN BONE GRAFTS BY MEANS OF RADIOACTIVE PHOSPHORUS*

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THE STORAGE OF TISSUES, such as bone, skin, blood vessels and other organs for future transplantation has been increasing in use since Alexis Carrel[1] in 1912 first attempted to preserve these tissues in cold storage, plasma, and Ringer's solution. He transplanted cartilage and periosteum which had been kept in cold storage for 24 to 48 hours in dogs and found that the cartilage remained alive, and that the periosteum produced bone.

Haas,[2] in 1923, experimented with the viability of bone in various conditions. Bone was removed from a dog, then fractured. A certain amount of time was allowed to elapse before transplanting to another location in the same animal. Most of the bone was left exposed to air or kept at room temperature under sterile conditions, or in saline. Experimental results were poor, many of the animals dying within a few days. He made the statement that "preservation in cold storage would be more efficient in preserving the survival period of cells," but no work was carried out at that time to support the theory. He also concluded from his work that, "osteoblastic cells of bone will survive an exposure period of 19 hours in air at room temperature."

All modern work on the use of bone preserved by refrigeration is based on the studies by Inclan.[3] He preserved autogenous and homogenous grafts in citrated blood kept at different temperatures, and concluded that bone cells and bone tissue varied little or not at all from fresh bone, when studied histologically, depending upon the staining qualities of the cell as an indication of viability. Clinical and roentgenographic examinations of patients, where frozen autogenous grafts had been used, showed that the refrigerated bone had acted as any fresh transplanted bone would have done in the same operation. Other contributions have been made by Wilson,[4] Bush and Garber,[5, 6] Reynolds and Oliver,[7] and Coley.[8]

In a previous communication, two of the authors[9] described a technic employing the metabolism of radioactive istopes as a measure of viability of immediate autogenous bone and cartilage grafts. The data reported showed that these grafts existed as viable tissue from the time of transplantation, since they metabolize radioactive phosphorus (P^{32}) at about the same rate as control bone and cartilage, forming their own blood supply and integrating themselves as a vital part of the system from the time of transplantation.

* Read before the American Surgical Association, Colorado Springs, Colorado, April 19, 1950.

This study is an elaboration of Section III of that report presenting observation on the effects of refrigeration on the viability of autogenous bone grafts during storage and after transplantation, using the following technic.

The right ilia of normal, adult dogs weighing 10 to 12 Kg. were removed in one piece, stripped of periosteum and muscle, and divided into segments of approximately equal size, with a chisel. These bone chips, containing both medullary and cortical bone, were sealed in sterile containers and stored in a deep freeze unit at 0 degrees C. for periods of time ranging from two to six months.

The grafts were then implanted separately in the subcutaneous tissues of the anterior chest wall of the same animal from which they were originally taken, after they had regained room temperature. Immediately after implantation, the animal was given 200 microcuries of radioactive phosphorus, intravenously. At varying intervals the grafts were then removed simultaneously with control samples from the intact ilium and were assayed for their radioactive phosphorus content.

TABLE I.—*Assimilation of P^{32} by Boiled, Frozen and Control Bone Grafts Recorded in Counts per Minute per Gram. The Second Column Includes Corrected Figures for Decay of P^{32}.*

Days After Injection With P^{32}	Control Bone		Frozen Bone		Boiled Bone	
0	0	0	0	0	0	0
2	4840	5400	3140	3500	2860	3200
6	6800	9100	2520	3360	2120	2820
9	5050	7800	3770	5000	2160	3220
21	4130	11500	2240	6200	1200	3320
26	....	....	2470	8500	950	3260
37	2220	13000	1616	9500	510	3000

After five to seven days the grafts were found to be intimately associated with the tissues of the animal, and it was no longer easy to remove them without excising a portion of the surrounding tissue. This intimate association of the grafts with the tissues of the animal became more marked with time, and they ultimately became surrounded by a thin layer of cortical bone. In about three weeks time, the sharp corners and edges were seen to disappear, the grafts assuming the appearance of sesamoid bones. Their overall size became somewhat reduced. The length of time the bone was allowed to remain in the deep freeze unit before use apparently caused no variation in their behavior. Experiments were also carried out in which one half of the frozen chips were boiled for 45 minutes before they were implanted in the right chest wall, and viable, frozen grafts in the opposite chest wall. The boiled grafts differed from the viable grafts in that they did not become intimately associated with the surrounding tissues of the animal. A thick fibrous capsule was formed around the graft, but it could be shelled out very easily from its bed five weeks after implantation.

The bone samples, after removal from the experimental animal, were oven dried to prevent any loss due to spattering when they were later ashed at 700 degrees C. The residue was then put into solution with nitric acid to facilitate uniformity among samples. This procedure resulted in similar physical states for all samples, and, consequently, produced the least error in applying the counting method used.

After the specimens were properly prepared they were counted by an ordinary Geiger-Mueller counter, using the decade scaler. The Geiger tube had a window thickness of 3.2 mg. per square centimeter. The samples were recorded in terms of counts per minute per gram of bone.

The data presented in Table I has been corrected for physical decay (as recorded in the second column of figures) and therefore represents the actual biologic utilization of radiophosphorus. In this figure the differences in the rate of incorporation of P^{32} is clearly indicated in normal bone, boiled bone and frozen implants.

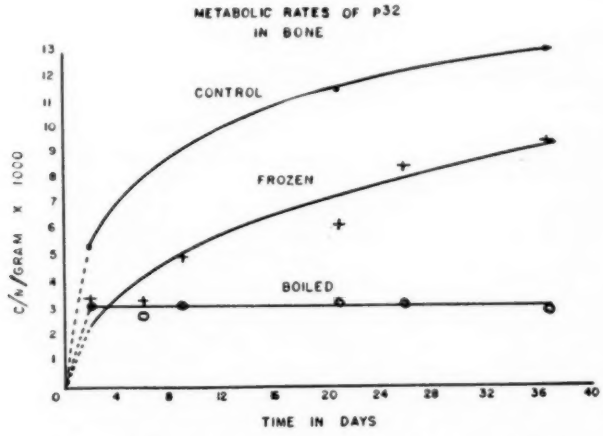

FIG. 1.—Graph representing assimilation of P^{32} in boiled, frozen and control bone grafts.

The rate of uptake of radiophosphorus appears almost surely to be related to the metabolic activity of the bone and begins as early as the second day. Boiled bone takes up some of the P^{32} (probably by simple inorganic exchange) and compares favorably with the observation stated previously that there is a fibrous tissue capsule and a foreign body reaction around the devital bone. This lack of vascularization prevents the incorporation of the isotope into the boiled graft and this is demonstrated by the fact that the curve is almost flat for the entire length of time it remained in the animal, as seen in Figure 1.

The curves of the control and frozen bone implants continue to rise from the beginning, indicating clear-cut utilization of the available phosphorus. The rate of utilization of P^{32} in both the control and frozen bone appears to be similar, since the curves have approximately the same slope. The frozen

bone implant, however, never reaches the level observed in the control bone. This is apparently due to the fact that the blood supply to the graft is not completely established and does not permit the rapid exchange of metabolites which would occur in the control bone.

CONCLUSIONS

It may be concluded from the above data that devital or boiled bone does not metabolize P^{32}, since the curve remains stable. This finding seems to justify the assumption that there is no tissue fluid exchange to and from the graft which does not become integrated or vascularized as part of the body.

Autogenous frozen bone grafts do exist as viable tissue when implanted after storage at 0 degrees centigrade as long as six weeks. They not only exhibit metabolism of P^{32} but also incorporate P^{32} at approximately the same rate as controls.

Further studies are being carried out with homogenous bone, varying the isotope, the temperature and the length of time the grafts are stored.

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DISCUSSION.—DR. J. ALBERT KEY: Like a good many other people, I have been interested in the transplantation of tissue for quite a long time. When I was an intern with Dr. Osgood in Boston in 1920, I started trying to transplant dead tendons. The "nigger in the woodpile" was that with the microscope we couldn't tell what was dead and what was living.

Recently Dr. Mueller and Dr. Odell and I (they have been doing most of the work, of course) have been doing similar experiments to this, except that we used homogenous grafts in bone rather than in the chest or abdominal wall.

There is no question in the minds of a lot of people—of whom I am one—that when autogenous bone is transplanted, some of the cells live and some of the bone lives, and the interior dies, and the grafts are later replaced by creeping replacement as Dr. Phemister has shown. With homogenous grafts there is no survival of cells or bone.

With homogenous preserved grafts you may get appositional bone laid down that impresses you that this is growth from the graft. Concerning the taking up of P-32 by the graft: is this metabolism? Do the living cells which have been taken out of an environment of nice, warm, red blood and put in an icebox at zero degrees Centigrade for six weeks survive? If you immerse your toe in fluid at a temperature of zero degrees Centigrade, it doesn't come back—and it doesn't take six weeks.

Our experiments are going to be reported next month at the American Orthopedic Association. The results are not as uniform as these, because we go off on a tangent every once in a while, and the whole thing seems to go haywire. But, we do not believe that the taking up of P^{32} by the graft is due to metabolism or is evidence of viability. We believe that the P^{32} is adsorbed by the graft and that there is an exchange of P^{32} ions in the surrounding medium and the P^{31} in the graft. The amount of this exchange is a function of the surface exposed to the medium and this varies with different forms of grafts and is greatest in the autogenous (living) grafts. Apparently the denaturization of the protein in the graft by boiling or by chemical means interferes with the reaching of the internal surface by the surrounding fluid and thus lessens the absorption of P^{32} in the graft.

Dr. Clifford L. Kiehn (in closing): Dr. Key states that his results are not as uniform as ours. Well, one reason is that he is using homogenous grafts and we are using autogenous grafts. Anybody can get uniform results with autogenous grafts, I feel, but when you start dealing with homogenous grafts, then I don't think anybody can get uniform results, whether by X-raying, clinical evidence, isotopes or any method. It is a problem deeper than we are considering here tonight. There are many variables in this study, and I would like to show a couple of slides on this, if I may.

[Slide] He also mentioned the question of storage. I do not feel that these methods that we are using today are ideal at all, and I think that the method used by Gross in Boston, and some of these other methods, are probably better. But here is a variable that we have to contend with: This is a cross-section of a femur in a dog after he has had P^{32}.

This shows the cortical bone on the outside, and the medullary bone on the inside, and shows the distribution of the P^{32} in the cancellous bone as compared to the distribution in the cortical bone. Right there it shows you how much of a variable you can get.

[Slide] Consequently, the more cancellous bone, the more isotopes will be taken up, because the circulation is better.

These are sections of ribs from the same dog. These are radio-autographs, in which the pieces of bone are laid on X-ray film in a dark room and allowed to expose the film by themselves.

This shows the distribution of the P^{32} in the ribs, and you can see that a rib or ilium with more cancellous bone would take better than a cortical bone.

[Slide] This one shows a radio-autograph, again, of aviable autogenous bone graft in which the isotopes are diffuse and very equally distributed throughout.

On the other side is a boiled piece of bone, in which the isotope is not completely diffused throughout the entire piece of bone. These samples are both of the same weight, and have approximately the same cortical and medullary constituents.

RESULTS OF TREATMENT OF SUBACROMIAL BURSITIS IN THREE HUNDRED FORTY CASES*

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SUBACROMIAL OR SUBDELTOID BURSITIS, long recognized as a clinical entity, is manifested by acute, subacute and chronic symptoms referable to the shoulder and arm and caused by lesions in the muscular tendinous cuff over the head of the humerus and in the subacromial bursa. Patients afflicted with subacromial bursitis tend to recover spontaneously, the time required for recovery varying from a few weeks up to two or three years, depending upon the nature and stage of the lesion. However, in many the symptoms are so severe or so annoying that the majority of patients seek treatment for relief. Among the many therapeutic measures used from time to time are simple and complicated applications of heat, injections of the bursa and adjacent nerves, roentgen therapy and incisions for relief of tension and removal of calcified deposits from the supraspinatus tendon and subacromial bursa. The fact that such varied forms of treatment have been recommended for the same condition strongly suggests that none is specific.

Reports in the current literature on the results of various methods of treatment usually have been based on small groups of cases with short periods of follow-up observation. In an attempt to increase our knowledge of the treatment of subacromial bursitis, we reviewed the records of 485 patients treated in the Ochsner Clinic for this condition during the seven-year period ending July, 1949. Follow-up information was obtained by questionnaire on 340 patients and these data have been analyzed in an attempt to evaluate the various methods of treatment employed. The average time elapsed between our first examination and the follow-up report was three years.

PATHOGENESIS

The present concept of the pathogenesis of subacromial bursitis is based on the work of Codman[1] together with recent reports of Neviaser[2, 3] on adhesive capsulitis or the "frozen shoulder." Codman described the underlying pathologic changes as consisting of degeneration in the collagen of the tendinous fibers unaccompanied by invasion of lymphocytes, leukocytes or other usual inflammatory signs. These changes occur near the insertion of the supraspinatus tendon where it lies beneath the floor of the subacromial bursa. As these degenerative changes progress, the tendon is weakened and

* Read before the American Surgical Association, Colorado Springs, Colorado, April 19, 1950.

complete rupture may occur with sudden, forcible abduction of the arm, giving rise to the classic symptoms and signs described by Codman.

However, in a large proportion of cases that begin as tendinitis, complete rupture does not occur (Fig. 1). Calcified deposits may appear in the tendon as its fibers degenerate and separate and, as these accumulate, minor strains or muscular efforts may suffice to aggravate the lesion. Fluid forms around the deposits and soon produces sufficient tension within the tendon to cause severe pain and spasm of the muscles about the shoulder. Although the inflammatory reaction spreads upward through the floor of the bursa and may involve the entire lining membrane, most of the pain is still caused by

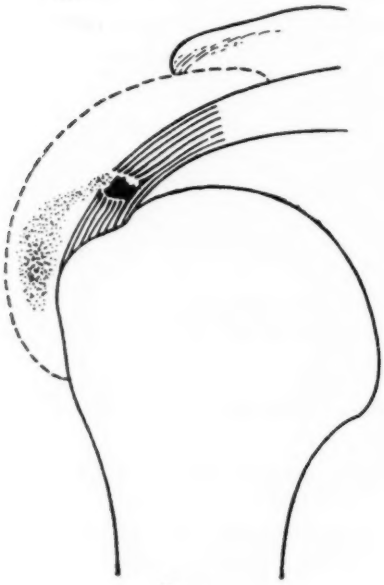

FIG. 1

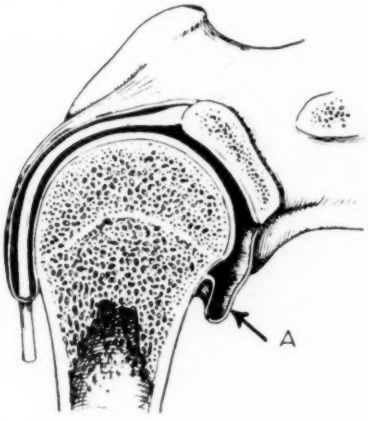

FIG. 2

FIG. 1.—Schematic representation of tendinitis with a calcified deposit that has ruptured into the subacromial bursa (Courtesy of Codman[1]).
FIG. 2.—Adhesions in the dependent part of the capsule which restrict movements of the shoulder (Courtesy of Neviaser[3]).

the excessive tension within the tendon. Release of this tension by spontaneous rupture, incision or puncture with a needle promptly relieves the severe pain. Although the fluid and calcified contents may then escape and lie free in the bursa itself for some time thereafter, there is only moderate pain and soreness in the shoulder and this usually subsides within seven to ten days. Occasionally this latter phase is prolonged, perhaps because the tension is not fully relieved. In such cases shoulder movements become increasingly restricted and the condition becomes chronic. This is known as the "frozen shoulder."

The early stage of tendinitis may not proceed to rupture or calcification and subsequent acute subacromial bursitis but, instead, may persist as simple

tendinitis without calcification. Small rice-like bodies and some clear fluid appear within the tendon and gradually produce mild aching pain and "catches" in the shoulder, with progressive limitation of the movements of abduction and external rotation (Fig. 2). In such cases the course is likely to be chronic and to terminate in adhesive capsulitis, as described by Neviaser, or in the "frozen shoulder" portrayed by Codman.

CLASSIFICATION OF CASES

Although we realize that the foregoing classification by Codman is correct from the viewpoint of pathogenesis, we classified our cases clinically according to the severity and duration of symptoms into three groups: acute, subacute and chronic. Acute cases included those patients with sudden onset of severe pain in the shoulder accompanied by spasm of the surrounding muscles and acute tenderness over the bursa which persisted for one to four weeks. The subacute cases included those whose symptoms were milder but persisted from one to six months, with aching pain in the shoulder, and moderate limitation of shoulder movements but little or no localized tenderness over the bursa. The chronic group consisted of those with symptoms of more than six

TABLE I.—*Distribution According to Age, Sex and Calcified Deposits in 485 Cases of Subacromial Bursitis*

Stage	Sex M.	Sex F.	Average Age Years	Calcified Deposits	Total
Acute—1–4 weeks.....	60	75	44.5	64 (47%)	135
Subacute—1–6 months...	77	74	46.1	59 (39%)	151
Chronic—over 6 months..	84	115	48.4	91 (45%)	199

months' duration. Shoulder movements were limited to 45° abduction with little or no internal or external rotation; the muscles about the shoulder were atrophied; there was no localized tenderness and pain was greatest at night. As far as we have been able to diagnose them, cases with rupture of the supraspinatus tendon have been omitted. Each group in our series included cases with and without calcified deposits in the supraspinatus tendon or the subacromial bursa. However, the chronic group corresponds to the "frozen shoulder" described by Codman or the adhesive capsulitis of Neviaser.

Of the 485 patients examined, 135, or 28 per cent, had acute subacromial bursitis, 151, or 31 per cent, had subacute and 199, or 41 per cent, had chronic subacromial bursitis (Table I). It is probably fair to assume that most of these patients had some kind of treatment in the early stages, but such treatment was apparently not effective in 41 per cent of cases. As can be seen in Table I, there was no significant difference between the sex incidence in the acute and subacute groups but in the chronic group there were 31 more females (16 per cent) than males. The average age in the chronic group was 48.4 years, whereas it was 46.1 years in the subacute and 44.5 years in the acute group. Calcified deposits were present in the supraspinatus tendon or in

the subacromial bursa in 39 to 47 per cent of cases, there being no significant differences relating to the three stages.

TREATMENT

The various types of treatment in this series were administered or prescribed by seven different surgeons in the Orthopedic Department. Our general attitude has been that with conservative nonoperative measures most patients will become reasonably comfortable and gain fair use of the arm within a few weeks. The principal aim has been to relieve the acute pain as soon as possible and then to preserve motion or to overcome such adhesions as were already present by the use of heat, followed by stretching exercises.

Procaine Injections. Complete relief of some of the most acute symptoms was promptly obtained after injection of a 1 per cent solution of procaine hydrochloride into the skin, muscle and bursa, followed by multiple punctures of the tendon near its insertion into the tuberosity. Success in some of the acute cases led to use of the same procedure in some of the patients in the subacute and chronic groups.

Physical Therapy. As a rule most patients were also advised to have some form of heat applied to the shoulder, followed by gentle massage to relax the muscles, and then to practice circumduction movements and other stretching exercises to combat the formation of adhesions. Heat, massage and stretching exercises have been indicated in the accompanying tables as physical therapy, whether carried out at home or by a physical therapist. However, most patients who had physical therapy only, were treated by an experienced physical therapist, at least until the patient became reasonably comfortable and had mastered the technic of doing the exercises properly.

Roentgenotherapy combined with sedation has been used more and more by us to relieve severe pain when it occurs at any stage in the course of subacromial bursitis. However, it seems to be most effective in the initial attacks of the acute stage. The use of roentgenotherapy is empirical. It seems to us that the most rational explanation of the action of roentgen rays is that they produce *active* hyperemia about the periphery of the area of congestion or *passive* hyperemia. The increased vascularity thus induced around the lesion tends to relieve the congestion and reduce the tension within the tendon. Most lesions so treated seem to resolve without rupturing into the bursa because the relief of pain is not sudden, but is gradual. After the acute pain has been alleviated by two or three radiation treatments, we then prescribe the same physical therapy measures as in other cases.

Incision. Release of tension by opening the bursa and incising the supraspinatus tendon, followed by removal of calcified deposits, was reserved for the most acute cases, those in which relief was not obtained by more conservative measures and the chronic or recurrent cases. After incision of the tendon the shoulder was manipulated gently to establish a full range of motion, and suspension or traction was applied to the arm for one to two

weeks postoperatively. Stretching exercises were employed while the patient was in bed and continued after the patient was dismissed from the hospital.

Manipulation. Manipulation under anesthesia was carried out in a few of the chronic "frozen shoulders," which did not have calcified deposits. Manipulation was usually done at one sitting, and a complete range of motion was re-established. In most of the patients so treated the shoulder yielded readily with the separation of only one or two strong bands of adhesions. The immediate postoperative reaction was usually not severe, and great improvement in the range of motion continued for a few days. However, in spite of suspension and traction, and voluntary and assisted active exercises, most of the shoulder movements gradually became more limited and the net gain was small, although the associated pain was often considerably lessened.

RESULTS OF TREATMENT

The results were tabulated from questionnaires returned by 340 patients. The questions related to (1) the length of time before all pain disappeared, (2) recurrence, (3) treatment received elsewhere, (4) present range of shoulder movements as determined by (a) ability to reach equally high on the wall with both hands, (b) ability to reach back of the neck equally well with either hand, and (c) for women, ability to fasten brassieres. Whereas Table I presents the data obtained from the records of 485 patients examined at the Ochsner Clinic, the subsequent tables represent the results obtained in the 340 patients in whom follow-up data were obtained. Inasmuch as several patients had involvement of both shoulders, the figures indicate the results obtained in the shoulders treated; for this reason, the totals do not correspond to the total number of patients reported.

Grading of Results. The result was considered *good* if the patient had no pain, no recurrence and no limitation of the shoulder movements, *fair* if he had slight limitation of one or more of the shoulder movements, with intermittent pain or soreness but no recurrence of severe pain and muscular spasm, and *poor* if he had persistent pain and considerable limitation of all shoulder movements with or without recurrence of acute episodes of pain and muscular spasm. The results rated as *fair* were considered *satisfactory* by most patients, in that they were relieved of the constant severe pain and had recovered a useful range of shoulder motion which permitted them to carry on their daily routine with little annoyance. Therefore, in regard to the overall picture of results, those rated as good and fair might be combined in one group which might be termed *satisfactory*.

Results in Acute Stage. Four different kinds of treatment were used in the management of 136 shoulders with acute symptoms during the first week after onset (Table II). Only four of these shoulders were subjected to operation with good results in three and fair in one. Other methods employed were injections of a 1 per cent solution of procaine hydrochloride with or without physical therapy, roentgenotherapy with or without physical therapy,

or physical therapy alone. There was no significant difference in the results obtained by these different measures, although the percentage of poor results (8 per cent) from roentgenotherapy was appreciably less than from other methods. If the good and fair results are combined into one group as *satisfactory*, it will be seen that in 118 shoulders, or 87 per cent, the results were satisfactory, whereas in only 18, or 13 per cent, the results were poor.

Results in Subacute Stage. The same methods of treatment, with the exception of incision, were employed for this group as for the acute group.

TABLE II.—*Results of Therapy in Acute Stage of Subacromial Bursitis in 136 Shoulders*

Therapy	Good	Fair	Poor	Cases
Procaine ± physical	15	4	7	26
Roentgen ray ± physical	56	20	7	83
Physical only	13	6	4	23
Incision only	3	1	0	4
Total	87	31	18	136

It is noteworthy that treatment of 16 shoulders by procaine injections gave good results in only four, or 25 per cent, and poor results in seven, or 44 per cent. However, the results for roentgenotherapy and physical therapy alone were equally as good as in the acute group, and again, if the good and fair results are considered as satisfactory, it will be seen that results were satisfactory in 87, or 84 per cent, of 103 shoulders.

Results in Chronic Stage. In addition to the measures employed for treatment of the acute group, manipulation under anesthesia followed by suspension, traction and shoulder exercises was employed in seven patients

TABLE III.—*Results of Therapy in Subacute Stage of Subacromial Bursitis in 103 Shoulders*

Therapy	Good	Fair	Poor	Total
Procaine ± physical	4	5	7	16
Roentgen ray ± physical	35	14	6	55
Physical only	20	9	3	32
Total	59	28	16	103

(Table IV). Following manipulation there were no good results; four were graded fair and three poor. Therefore, this form of treatment, in our hands, leaves much to be desired. Surprisingly, of nine shoulders that were incised, good results were obtained in six and fair in three; these results are as good or better than those obtained in the acute group by the same procedure. There was no significant difference in the results obtained by the other three measures, but approximately 33 per cent of the results in the entire group were poor; this is a much higher percentage than in either of the preceding groups.

DISCUSSION

As the three tables showing results of the various treatments according to the stage of the disease indicate, the same three conservative measures (procaine injection, roentgenotherapy and physical therapy) were used to treat the majority of patients regardless of the stage of the disease. Table V shows an evaluation of the results of the various kinds of treatment employed without regard to the stage in which treatment was given. These statistics suggest that the combination of roentgen ray with physical therapy gives the best results, since in only 15 per cent were the results poor.

TABLE IV.—*Results of Therapy in Chronic Stage of Subacromial Bursitis in 138 Shoulders*

Therapy	Good	Fair	Poor	Total
Procaine ± physical	7	3	6	16
Roentgen ray ± physical	23	18	17	58
Physical only	13	18	17	48
Incision	6	3	0	9
Manipulation ± traction	0	4	3	7
Total	49	46	43	138

It should be noted that the common denominator for all three treatments has been physical therapy, which is indicated to maintain or increase the range of shoulder movements. Roentgenotherapy cannot be expected to accomplish more than relief of pain and muscular spasm induced by pain. Therefore, if restricted shoulder movements persist after pain has subsided, one must assume that adhesions are the cause. If the limitations are less than 50 per cent of the normal range of movements and only two or three weeks

TABLE V.—*Results of Therapy in Subacromial Bursitis in 357 Shoulders Without Regard to Stage of Disease*

Therapy	Good	Fair	Poor		Total
			Cases	%	
Procaine ± physical	26	12	20	34	58
Roentgen ± physical	114	52	30	15	196
Physical only	46	33	24	23	103
Total	186	97	74	20	357

have elapsed since the acute phase, one may expect a well-supervised program of exercises to be effective. However, when the shoulder movements have been restricted more than 50 per cent for a month or more after the acute phase has subsided, it is unlikely that exercises alone will suffice. The results obtained from manipulation under anesthesia are discouraging, whereas incision with removal of calcified deposits and Neviaser's added procedure of cutting across the inferior portion of the capsules of the shoulder and freeing it from the head of the humerus, gives greater promise of relieving the cause of the trouble. This procedure should be followed by

systematic exercises for two to three months postoperatively if a full range of motion is to be regained.

Calcified Deposits. Calcified deposits were found in 155 or 44 per cent of 349 shoulders. There was no apparent relation to the stage of the disease. Recurrent, acute attacks may be expected in 22 per cent of the acute and subacute cases and in 33 per cent of the chronic cases.

Acute attacks recurred in 41, or 27 per cent, of the 155 shoulders, with calcified deposits and in 39, or 20 per cent, of the 194 shoulders without such deposits. These figures suggest that the presence or absence of calcified deposits probably has little or no bearing upon the recurrence of acute attacks. The calcium appears to be a bi-product of the degenerative lesion in the supraspinatus tendon, but is neither a cause of the lesion nor of the symptoms which accompany it.

SUMMARY

The records of 485 patients with subacromial bursitis treated in the Ochsner Clinic during the seven-year period ending July, 1949, were analyzed in an effort to evaluate the various methods of treatment employed. The treatments most used, regardless of the stage of the disease, were procaine injections and roentgenotherapy, each supplemented by physical therapy; some patients were treated with physical therapy alone. Follow-up reports of the results obtained on 340 patients after an average period of three years were analyzed with reference to stage of the disease at the time treatment was given. Analysis of these results indicates that:

1. Satisfactory relief of pain and restoration of a useful range of motion may be obtained by conservative measures in 70 to 85 per cent of cases.

2. Roentgen therapy is an effective measure for the relief of pain produced by tension within the supraspinatus tendon in 85 per cent of cases.

3. Physical therapy is a necessary adjunct to all other measures that may be employed. Physical therapy alone is adequate for many subacute or mild chronic cases.

4. Recurrent attacks are to be anticipated in 22 per cent of cases following acute or subacute symptoms and in 33 per cent of patients with chronic symptoms.

5. The presence or absence of calcified deposits seems to have no relation to the various stages nor to the incidence of recurrent attacks.

6. The longer the symptoms have persisted the poorer the outlook for relief by conservative measures. In the chronic group of cases 33 per cent had poor results.

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Discussion.—Dr. Kellogg Speed: We are thankful that this all too common, distressing condition has been brought to our attention. At the Presbyterian Hospital in Chicago, in the past five years, there has been an average of 300 out-patients per annum who have been treated for painful shoulder in the X-ray department, going directly there in most instances. The permanent relief in that group has been over 80 per cent. In that period I have injected over 200 shoulders with procaine and operated upon 35 with calcific deposits.

I cannot refrain from calling to your attention that the basic anatomic and pathologic information about painful shoulder was first completely reported by Professor Meyer of Leland Stanford University in 1937. We may agree with him that the shoulder is a marvelous mechanism—the demands we make upon it call for a universal joint—but it is not, however, quite perfectly adapted to these demands, and hence is subject to stresses and strains and wear in everyday use.

Dr. Caldwell cites some of the results of these uses, which must include some trauma to the surrounding parts. As they recur, hour by hour, in active life, endarteritis and sclerosis are set up in some of the tissues, and a cumulative effect results from the constant irritation, whether the use of the shoulder involves a full range of the joint (as in the case of the baseball pitcher) or in a repetition of lessened character and range of motion. Therefore, most of these lesions are rare before the third decade of life, as shown by his figures.

Dr. Meyer, listing 13 different lesions about the shoulder, calls attention to the fact that the lesions are traumatic in the final analysis, and are the result of quantitative rather than qualitative insults. We may therefore believe that Codman was wrong in arguing that these painful shoulder lesions were based on rupture of the normal tendon of the supraspinatus, the insertion of which into the humerus is three-quarters of an inch long. This tendon has a tensile strength many times that of its muscle belly, and can bear an estimated pull of 700 pounds before rupture, while the muscle belly can stand only 170 pounds. This makes rupture of a sound, normal tendon by an active muscle very doubtful, and the tendon would show transverse tears instead of longitudinal splits and trabecular frayings constantly found. Some of these degenerative processes were described by our colleague, Albert Key, in his address before the Southern Surgical Society last year.

In a study of 1000 cadavers, Meyer found no thickened bursal wall, no chronic inflammation, no effusion or adhesion. The process as he described it is a "use destruction" of the inner layer of the connective tissue of the joint and bursal lining, but this would not apply to gouty shoulders.

Bursal irritations, therefore, are of varying degree, down to those accompanied by deposit or calcific material, and any treatment which leads to obliteration and adherence of the lining surfaces—and yet maintains a full range of motion of the joint—may give symptomatic cure. Pain may be permanently dissipated by X-ray treatment or procaine injection, although a calcified deposit may remain in situ. Operation is therefore indicated only after trying non-operative methods, as Dr. Caldwell has mentioned, and that is the last word in cure because it eradicates the bursal sac.

Dr. J. Albert Key: I divide these shoulders into those with calcium and those that do not have calcium. A frozen shoulder without calcium is quite a problem. I prefer to treat the ones with the calcium deposit because I can do something for them. They will get well by themselves if you leave them alone, but some of them last a long time and may leave a stiff and painful shoulder.

If you expose the floor of the bursa in one of these acute, fulminating shoulders, you will find a lesion which looks like a boil. The deposits are usually multiple, but only one of them is acutely inflamed.

The question is whether it is the inflammation that causes the pain or the tension. Sometimes the calcium in the deposit is under considerable tension.

Usually, when the deposit ruptures spontaneously into the bursa, the pain subsides. And that is what you do when you stick a needle in the nidus. However, I am not very good at hitting the lesion and frequently when I try to aspirate the calcium the patient's pain is aggravated and they have a very bad 48 hours. So, I do not do this any more unless I have them in the hospital.

About three years ago I was sued for $24,482 for a calcium deposit which I had operated on. About four months later the patient went to another surgeon and he found some more calcium in the shoulder. As this was not visible in the original X-rays I won the suit. But it should be stated here that no surgeon ever removes all of the calcium present when he operates for this purpose. To do so, it would be necessary to excise a considerable portion of the rotator cuff, and even then small foci might be overlooked. The surgeon removes the greater part of the calcium from the larger foci which he can identify, and expects the rest to be absorbed during the convalescent period.

No one has ever emphasized the fact that these deposits may be multiple. You may find a dozen of them in one shoulder ranging in size from the lower limits of ocular vision up to something as big as the end of your thumb, and the patient may have no pain. On the other hand, one little one may cause a lot of pain.

What the X-ray does to them, I still don't know. Many get well after X-ray treatment or no treatment, and others do not. Unless the symptoms are very acute I treat these lesions conservatively and the X-ray is one form of conservative treatment.

Several years ago, Smith-Petersen resected the acromion in a sort of homeopathic manner for arthritis of the shoulder. I did a few of those for frozen shoulders and they were not good. Recently J. R. Armstrong has reported a series of cases in which he removed the entire acromion with excellent results. I think that this is an operation we will have to do more and more in the future.

Given a patient with an acutely painful calcium deposit in the shoulder, I do not think that there is anything that is as satisfactory to the patient and to the surgeon as opening the bursa and evacuating the calcium. This relieves them in about five or six hours in practically every case.

Dr. James M. Mason, III: I cannot discuss this subject in the light of any large series of cases comparable to those of the preceding speakers, but we have been impressed nonetheless with the seriousness of this ailment and the misery which it causes.

In regard to the acute phase, one point seems worthy of emphasis: One is often called to see these patients at a rather late stage, after several days have elapsed, and when they have been treated with narcotics and sedatives to the extent that hospitalization is necessary for the clearing up of their sensorium and correction of dehydration. If these patients are seen early they can be treated immediately by injection at home, in the office, or in the out-patient department of the hospital without resorting to over sedation.

Dr. Caldwell used the term procaine. I would like to ask him if he condones the use of oily suspensions of procaine. The effects from the aqueous solutions have been so transient that we have of necessity used one of the oily solutions, usually Nupercaine in oil, with good results.

In the subacute phase, when an X-ray shows a calcium deposit in the bursa, we have not hesitated to make an incision and evacuate the deposit.

In a relatively small series, we have not had to manipulate a shoulder under anesthesia and have gotten good results with the use of deep X-ray therapy.

Dr. Guy A. Caldwell (in closing): I wish to thank Dr. Speed for adding the pathology as Meyer described it. I personally visualize the condition more as Codman

described it, but certainly there is a more diffuse picture in many cases that probably justifies the description as Meyer gave it.

No meeting would be complete without Dr. Key's discussion, and he gets better as he gets older. I would like to give him a little friendly advice, though—that if he wouldn't rush in to operate so fast, he wouldn't be sued so often. Moreover, if he will read Codman's description again, he will find that Codman described the multiple deposits, and said that when he had failed to relieve the patient by incising one deposit, he always expected to go back and find another one which he had overlooked.

Certainly, though, this is a perplexing subject, and I anticipated that there would be further discussion of treatment.

In the light of the series that we have reviewed, I have projected for future treatment some such plan as this: In acute cases we will continue to give roentgen therapy, followed by exercises, knowing from the experience we have had that nearly 92 per cent of them are going to do very well. However, there will be a few of these who do not do well, and after four to six weeks we are going to do something else for them.

With the subacute cases in which the onset has been rather insidious and in those acute cases in which relief by the first plan of treatment has been incomplete, I think the emphasis should be on intensive, well supervised physical therapy. Our own group, as we reviewed them carefully, certainly shows that well directed exercises accomplish a great deal; the results were good in 85 per cent of cases.

It is the chronic group that gives us all a headache, and when patients come to us with the condition already in the chronic stage, what can be done for them?

I think Dr. Key started to break them down in groups but did not describe all of them. I think there is a group that has a fair range of motion, in which pain is not a dominant factor—perhaps only a little pain at night. These should do very well on a good regimen of physical therapy. I believe Dr. Key should send all such cases to the physical therapist, and if he does so he will not have to rush them to the operating room.

Pain and severe limitation of motion, with calcification, certainly calls for exploration; I think we will all agree on that. Those who do not have calcification also should probably have an exploratory operation. I have found ruptured supraspinatus tendons. If we do not find a ruptured tendon, I still like to incise the tendon and may find only degenerated fibers and clear fluid. Although I have not been doing so, I now believe we might adopt Neviaser's procedure of incising the inferior portion of the capsule, stripping it away from the head of the humerus, rather than doing a vigorous manipulation. All the foregoing procedures will have to be followed by physical therapy and exercises.

AC-GLOBULIN LEVELS IN THROMBO-EMBOLISM*

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THE USE OF ANTICOAGULANTS in the prevention of thrombo-embolism has been an important addition to the armamentarium of the physician and the surgeon. In both experimental animals and human beings their administration has been accompanied by a significant and gratifying reduction in the expected incidence of intravascular clotting. Properly controlled anticoagulant therapy, however, is not inexpensive, it requires the attention of one familiar with its requirements and hazards, and hence is not at the present time practical as a routine postoperative procedure. The anticipation of thrombo-embolism which provides for the prophylactic use of anticoagulants in selected cases is highly desirable. The etiologic factors, however, remain obscure, and until they are clearly understood, the treatment of intravascular clotting is not likely to be completely satisfactory.

Many patients of all ages undergo major surgical procedures or are victims of various diseases without developing evidence of thrombosis or embolism. Others with apparently similar physical and nutritional states have thromboses and emboli of varying importance following similar surgical or medical experiences. It would seem reasonable, therefore, that variations in one or more of the coagulation or anti-coagulation factors might be responsible for such different responses.

Normally, the equilibrium between these clotting and anti-clotting factors seems to be in proper balance, protecting the individual against excessive bleeding on one extreme and excessive clotting on the other. In recent years our knowledge of certain of these factors has increased considerably. It was almost 50 years ago that Morawitz[1] proposed that blood clots in two stages (Fig. 1). In the first stage, prothrombin, thromboplastin and calcium interact to form thrombin. In the second phase, thrombin acts on fibrinogen to convert it to the relatively insoluble fibrin which is the clot. This theory stood without appreciable change until 1944 when Owren[2] discovered another factor which, he demonstrated, was essential to the normal physiologic clotting process, and which he called the fifth coagulation factor, or Factor V. Working independently, Fantl and Nance[3] and Ware, Guest and Seegers[4] discovered the same factor, the latter group demonstrating the mechanism of its action and

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calling it "accelerator globulin" or ac-globulin. The labile factor described by Quick is considered to be the same principle as Factor V and ac-globulin. At the present time, these five factors, *i.e.*, prothrombin, thromboplastin, calcium, ac-globulin and fibrinogen are considered the only ones essential to the physiologic clotting of blood. There are, however, certain anti-clotting factors which have to do with the coagulation mechanism. Those presently known are heparin,[5] anti-thrombin,[6] and antithromboplastin[7, 8] (Fig. 1).

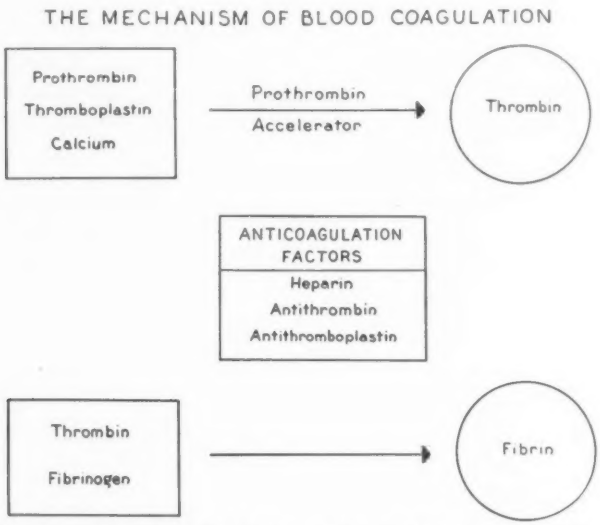

FIG. 1.—The classical theory of the mechanism of blood coagulation provides for two distinct phases of the process. In the first phase prothrombin, thromboplastin and calcium, in the presence of the recently discovered prothrombin accelerator (Factor V, ac-globulin, labile factor) interact to form thrombin. In the second phase the thrombin converts fibrinogen to fibrin. Acting physiologically or pathologically as antagonists to this process are the known anticoagulation factors, heparin, antithrombin and antithromboplastin.

At the present time there is certain specific information as to the role of several of the factors in bleeding tendencies, namely, abnormalities in prothrombin, heparin or heparin-like substances, platelets and fibrinogen. There is, however, relatively little knowledge as to the role each individual factor plays in hyper-coagulation tendencies. Measured changes in calcium and fibrinogen have not been significant in thrombo-embolism. There is as yet no satisfactory measure for thromboplastin, and information on this factor is meager. Increase in plasma prothrombin is of questionable significance as an etiologic factor in thrombosis, in the authors' experience, there being no uniformity in the level of prothrombin and the incidence of intravascular clotting. Recently Kay and Ochsner,[9] have found a low anti-thrombin in cases of thrombo-embolism and a reduction in the postoperative incidence of such con-

ditions by the elevation of this anti-clotting factor with alpha tocopherol and calcium. The role of heparin and antithromboplastin in the normal and pathologic clotting states is gradually being elucidated but is as yet not clearly understood.

Regarding the mechanism of ac-globulin action, Ware and Seegers[10] have shown that when relatively pure prothrombin is allowed to interact with thromboplastin and calcium in the absence of ac-globulin, thrombin is formed slowly over a period of hours. If, however, a small amount of ac-globulin is

TABLE I.—*The Role of Ac-globulin in the Clotting Process as Suggested by Ware and Seegers. During the So-called Induction Phase, i.e., the Interval Between the Shedding of Blood and the Visible Formation of the Clot, Three Distinct Processes Occur. Prothrombin, Thromboplastin and Calcium Interact to Form a Small Amount of Thrombin. This serves to Convert the Inactive or Precursor Plasma Ac-globulin to the Active Form, i.e., Serum Ac-globulin. The Latter Then Hastens the Formation of Large Amounts of Thrombin Which Initiates the Second, or Visible Phase of the Clotting Process, the Conversion of Fibrinogen to Fibrin.*

Induction phase of coagulation—4 to 10 minutes	
Prothrombin + Thromboplastin + Calcium	Thrombin (in small amounts)
Plasma Ac-globulin + Thrombin (small amounts)	Serum Ac-globulin
Prothrombin + Thromboplastin + Calcium + Serum Ac-globulin	Thrombin (large amounts)
Active phase of coagulation	
Thrombin + Fibrinogen	Fibrin

added, the reaction takes place in a matter of minutes, the rate of such reaction, and, up to a certain point, the amount of thrombin formed being relatively proportional to the amount of ac-globulin present.

They have found the accelerator present in both plasma and serum, but it has different characteristics in the two media, the plasma type being the inactive or precursor form, and the serum type the active form of the factor, that is, the real accelerator of prothrombin conversion. They have also found that thrombin in small amounts will activate plasma ac-globulin to serum ac-globulin. They suggest that at the initiation of clotting, a small amount of thrombin is formed over a period of several minutes, during the so-called

induction-phase of the coagulation of native or re-calcified plasma when fibrin formation is not yet apparent (Table I). Plasma ac-globulin is changed by the thrombin to its active fellow, serum ac-globulin, and the formation of large amounts of thrombin proceeds rapidly. This then converts fibrinogen to fibrin.

Under what conditions does plasma ac-globulin vary? Owren[2] discovered the factor by demonstrating its deficiency in a patient with bleeding tendency. It is known to disappear over a period of days in human citrated plasma stored at 5°C[12] and even more rapidly in oxalated plasma. Differences in the rate at which prothrombin is converted to thrombin in various species[13] can, in some instances, be related to differences in the amounts of ac-globulin in these plasmas.[14] McCormick and Young[15] found a significant elevation of the factor when large amounts of aminophylline were fed to dogs and Owren[16] found it elevated in several cases of thrombophlebitis. In liver disease[16] and in experimental liver damage[19] ac-globulin levels decrease in relation to the severity of the injury to the liver.

On the basis of such variations, both above and below the normal levels, and because of its key role in the rate of clot formation, it seemed reasonable that a study of this factor in intravascular clotting might be of interest. It is the purpose of this paper to report results of such a study in 46 patients with clinical evidence of thrombosis and/or embolism.

METHODS

The method described by Ware and Seegers[10] for measuring plasma ac-globulin was used. It is an adaptation of the two-stage prothrombin method of Warner, Brinkhous and Smith,[17] the prothrombin being rendered constant and the rate at which it is converted to thrombin being a measure of the ac-globulin present. Samples of blood were collected by venipuncture with the use of a 20-gauge needle. In order to reduce contamination by tissue fluids, the original 1 cc. of blood and syringe were discarded and a second clean, dry, syringe was attached to the needle. The blood was withdrawn and added immediately to the anticoagulant, one part of 3.2 per cent sodium citrate being mixed with nine parts of blood. Plasma was separated by centrifugation and stored at —35°C until removed for analysis. Ac-globulin has been found to be relatively stable for weeks under such conditions. Five samples and a control plasma were analyzed at the same time, the same reagents being used for all samples. Results were expressed in units of ac-globulin per cubic centimeter of plasma, and each unknown compared to the control plasma to give a final estimate in per cent of normal. In this study, 80 to 120 per cent was considered the normal range.

The series of 46 patients was selected as they appeared on the various services of the Presbyterian Hospital. They included 29 cases with thrombophlebitis or phlebothrombosis of the lower extremity, one with thrombophlebitis of the upper extremity following minor trauma, one with embolus to the

right leg, one patient with phlebothrombosis of the right superficial epigastric vein, three with thrombosis of the central retinal vein, one with cerebral thrombosis and five with coronary thrombosis. Two patients had clinically diagnosed pulmonary emboli without evidence of peripheral thrombosis or heart disease, and three others had pulmonary emboli apparently from the heart. Of the 30 patients with intravascular clotting in the extremities, one had a pulmonary embolus. None of the pulmonary emboli was fatal.

All patients received Dicumarol, and most, in the early stages of treatment, had heparin. In 30 cases, a pre-therapy, ac-globulin level was obtained. Determinations were made over varying periods of time up to three months. As few as one determination was made, and as many as 25, the average being seven. Fahey, Olwin and Ware[18] found that in dogs and human beings the ac-globulin often dropped in the early days of Dicumarol therapy to from 20 to 50 per cent below pre-therapy levels, returning to normal by the end of

TABLE II.—*The Distribution of Patients According to Their Highest Ac-globulin Levels, in Thrombo-embolism, After the Onset of Intravascular Clotting.*

	Per Cent of Normal	No. of Patients	Total
Normal range	80 to 90	1	
	90 to 100	3	
	100 to 110	3	
	110 to 120	2	9 (19.5%)
Above normal	120 to 130	7	
	130 to 140	10	
	140 to 150	1	
	150 to 160	6	
	160 to 170	4	
	170 to 180	3	
	180 to 190	4	
	190 to 200	0	
	200 to 210	2	37 (80.5%)

three weeks, even though the Dicumarol was continued and the prothrombin remained depressed. Such influence was apparent in this study and no doubt contributed to many of the lower readings. The elevated readings apparently occurred before this influence was manifest, after it disappeared, or in some instances in spite of it.

RESULTS

Of the 46 cases studied, 37, or 80.5 per cent, showed ac-globulin levels of 120 per cent or more at some time, in most instances, in the first week following the clinical onset. The highest level, 208 per cent, was found in a woman with acute thrombophlebitis of the leg following delivery. Nineteen cases, or 51 per cent of those showing abnormal elevations, had levels of 150 per cent or more. Thirteen patients had levels of 160 per cent or above, nine were above 170 per cent, and six were over 180 per cent. Two had a level of 200 per cent or more (Table II). Of the 30 on whom pre-therapy determinations were obtained, 22, or 73 per cent, had levels of 120 per cent or more.

DISCUSSION

It is not at once apparent whether the rise in ac-globulin found in cases of thrombo-embolic disease is a result rather than an etiologic factor in the thrombotic process. It should again be pointed out that the ac-globulin found in serum is a different type from that present in plasma,[11] and is considered the active form of the substance. In no instance was the "serum type curve" encountered. This would seem to be evidence in favor of a cause rather than effect status of the factor. Another possibility is that the ac-globulin elevation is a result of stimulation of the liver (probable site of ac-globulin formation)[19] by the thrombotic or other process and is thus a result of the thrombosis or, at most, coincidental to it. Conversely, the elevation might be due to an impairment of the process of removal or destruction of ac-globulin. The site of such process is not known.

Because intravascular clotting is quite probably influenced by a variety of conditions, such as stasis, infection, trauma, an excess of one of the coagulation proteins, or by a deficiency of one of the anti-coagulation factors, it is conceivable that a major abnormality in one of the clotting factors might not be constantly present in the thrombo-embolic state. The etiologic factors may vary in their proportion to one another in individual cases with the result that detectable alterations of one factor are present in only a portion of the cases.

The behavior of ac-globulin in the postoperative period might serve further to elucidate the possible role of this factor in the development of intravascular clotting. Such a study is in progress at the present time.

SUMMARY

In 46 patients clinically showing evidence of intravascular clotting, there was an elevation of the plasma ac-globulin in 37 or 80.5 per cent. In 51 per cent of those showing an abnormal rise, the ac-globulin was over 150 per cent of normal.

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AGNOGENIC VENOUS MESENTERIC THROMBOSIS*

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WITH THE INTRODUCTION OF THE ANTICOAGULANTS, surgery acquired valuable agents in the prevention and treatment of accidents and conditions associated with increased coagulability of the blood. Mesenteric thrombosis, always a terrifying abdominal emergency, usually finds both patient and surgeon unprepared for surgery of great magnitude, but its high operative mortality is still considerably lower than when operation is not performed. Diagnosis is difficult, and surgery frequently too long delayed, and this hesitancy still persists in spite of the advance in therapy afforded by the anticoagulants. In the past, authors have considered both the arterial and venous forms together. We wish, however, to focus entirely upon the venous variety and have restricted this still further so as to exclude all venous thromboses with known cause, which are quite distinct from primary agnogenic venous mesenteric thrombosis.

HISTORICAL REVIEW

Mesenteric thrombosis was first described by Antonio Beniviene in Florence in the latter part of the 15th century,[1] and although Joseph Hodgson reported a case from Guys Hospital in 1815,[2] it was not until Tiedman,[3] in 1843, and Virchow,[4] in 1847 and 1854, described this condition that the medical profession really became interested. In 1895, J. W. Elliot[5] of the Massachusetts General Hospital, Boston, reported the recovery of a patient following the "operative relief of gangrene of intestine due to occlusion of the mesenteric vessels." Dr. Elliot has left us an excellent description of what was probably a venous occlusion. The patient was an otherwise healthy male in his mid-forties who was operated upon early and made an uneventful recovery in the absence of any of our modern supportive therapy.

Since the turn of this century, numerous articles have appeared. In 1904 Jackson, Porter, and Quimby[6] collected 214 cases of arterial, venous and mixed thrombosis, 26 of which were new. The ages of the patients varied from *one month to 90 years*. In 1909 Welch wrote on mesenteric thrombosis in Allbutt and Rolleston's Medicine.[7] In 1913 Trotter[8] surveyed 360 cases with an age range between 30 and 70. The correct diagnosis was made preoperatively in 3.6 per cent and the operative mortality was 63.8 per cent; the thrombosis was described as venous in 41 per cent. In 1935 Donaldson and Stout[9] discussed venous mesenteric thrombosis as an entity separate from

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arterial thrombosis. They suggested that the venous form was "a slowly progressing condition" and in the early stages "most thoroughly amenable to surgery." Also in 1935, Warren and Eberhardt[10] presented 73 cases from the literature and two of their own of venous thrombosis. In discussing the etiology they listed four types:

1. Known infection, as thrombophlebitis, appendicitis, pelvic abscess, peritonitis, sepsis.

2. Hematogenous causation, as blood dyscrasias or changes known to predispose to thrombosis, such as splenic anemia and polycythemia vera.

3. Trauma of any sort to mesenteric veins.

4. Mechanical causes, such as portal stasis, pressure from tumors, adhesions and bands, volvulus.

In 1938 Whittaker and Pemberton[11] reported 60 cases of mesenteric thrombosis from the Mayo Clinic with 57 deaths. The youngest was 13 and the oldest 83 years of age; 27 per cent were venous.

Following the introduction of the anticoagulants the record has changed for the better, though progress has been slow. Murray,[12] in 1940, reported six cases of mesenteric thrombosis with two deaths. All were operated upon with resection of the involved area, 45 cm. to 7 meters, and all were treated with heparin postoperatively. D'Abreu and Humble[13] reported a similar case in 1946, and also described a rather ingenious heparin tolerance test which they employed.

Closely associated with the whole problem of mesenteric thrombosis is consideration of the blood circulation in the mesentery. This was brought to attention by Mayo-Robson in 1897,[14] and Wilms[15] in 1901, when they reported ligation of the superior mesenteric vein near the entrance of the right colic vein for wounds of the vein, with recovery of both patients. Twenty years before Solowieff[16] had shown that individual staged ligation of the superior mesenteric, splenic, and portal veins in dogs did not cause death. More recently Scott and Wangensteen[17]; Boyce and McFettridge[18]; and Noer and co-workers[19-21] have all studied this problem in its various phases; and Laufman,[22] working with heparin, found that in experimental occlusion of the superior mesenteric vein in dogs, or ligation of the vasa recti, there was a higher survival rate when heparin was used.

CASES

With this as a background we present 13 instances of agnogenic venous mesenteric thrombosis in 12 patients. Eleven of these cases are from the records of the Presbyterian Hospital, New York,* over the past 22 years. During this period 53 cases were classified as venous mesenteric thrombosis.

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Of these only 11 are true agnogenic; ten patients comprise this group as one had two episodes with a free interval of 32 months between attacks. One other, who developed the disease while in terminal coma from a brain tumor, is not included. These 11 cases occurred in 54,000 surgical admissions in this period, an incidence of 0.02 per cent. In the other 42 cases the possible causes are given, as listed, in Tables I and II.

TABLE I.—*Listed Causes of Venous Mesenteric Thrombosis, Other Than Agnogenic Variety, in 42 Patients, Presbyterian Hospital.*

Mechanical Obstruction	Intra-Abd. Tumors	Intra-Abd. Suppuration	Trauma
Cirrhosis..... 4	CA pancreas..... 4	Appendicitis..... 7	Sup. mes. vein... 1
Cong. portal malform 1	Mesothelioma..... 1	Chr. ulc. colitis with	
Volvulus..... 2	CA colon..... 3	abscess..... 1	
Strang. hernia..... 1	CA liver..... 1	Pelvic abscess..... 1	
Adhesions..... 5	Carcinoid..... 1	Postop. sepsis..... 2	
Schistosomiasis..... 1	Lymphosarcoma..... 1	Perf. viscus..... 1	
	Leiomyoma bowel... 1	Pancreatitis..... 1	

It may be of interest to record here that in 1932 McIver[23] reported from the Massachusetts General Hospital that 3 per cent of 355 cases of intestinal obstruction were caused by vascular occlusions in the mesentery.

Case 12 is from the Third Surgical Division, Bellevue Hospital,* and Case 13 is a patient from Gorgas Hospital,* Panama, seen by the senior author.

Four of these patients survived, one from two episodes. In all, operation with resection of the involved area was performed and anticoagulant therapy

TABLE II.—*Agnogenic Venous Mesenteric Thrombosis; Time of Onset to Admission and Surgery; Outcome.*

Case	Age	Sex	Onset: To Admission	Onset: To Surgery	Outcome
1.....	40	M	4 D	8 D	R
1A.....	43	M	6 H	30 H	R
2.....	30	F	40 H	62 H	Dead
3.....	39	M	7 D	7 D, 17 H	Dead
4.....	74	F	24 H	25 H	Dead*
5.....	58	F	14 D	None	Dead*
6.....	36	M	8 D	8 D	Dead
7.....	73	F	7 D	7 D	R
8.....	73	M	7 D	None	Dead
9.....	43	M	14 D	21 D	Dead
10.....	52	F	15 D	23 D	R
11.....	40	M	11 H	15 H	R
12.....	50	M	4 D	None	Dead

* Thrombosis portal vein. D = Days. H = Hours.

was used following surgery in four of the five successful cases. Although the histories are given in detail and the salient points shown in Tables II to VI, two of the patients are of unusual interest: Patient B. H., Case I and IA (778189) had seven Presbyterian Hospital admissions for migrating thrombophlebitis of his pelvic, arm and leg veins from 1935 to 1938, and from 1939

* See footnote on page 451.

to 1945 he was followed in the Clinic. After his eighth admission, his first attack of mesenteric thrombosis, he remained perfectly well for 32 months. On his ninth hospital admission, the second episode of mesenteric thrombosis, his condition was still sufficiently obscure that operation was delayed 24 hours. Anticoagulants were given during this second postoperative period and for the past two and a half years he has been kept on a maintenance dose of Dicumarol without further symptoms.

Patient A. R., Case 11 (BH 53967-48), had had three hospital admissions during the preceding 14 years for thrombophlebitis of the lower extremities, and home treatment for several minor attacks. Also, during his first hospital admission he had suffered a pulmonary infarction. His family history revealed that he had three brothers, and all of them had had repeated attacks of thrombophlebitis. Furthermore, two of his brothers had been operated upon for venous mesenteric thrombosis, one of whom recovered. The other, who also gave a history of a pulmonary infarction, made his own diagnosis, but, in spite of this, operation was delayed for 48 hours, no anticoagulant therapy was given, and he died on the second postoperative day. In view of this extraordinary family history, the patient thought that he too had a mesenteric thrombosis, which was proved at operation four hours after admission.

Case 1 and 1A.—B.H., 778189 was a male, age 43. During a 3-year period from 1935 to 1938 a post-office clerk afflicted with migrating thrombophlebitis was admitted to the Presbyterian Hospital 7 times with an average stay each time of 14 days. His exacerbations were treated with bed rest, elevation, fever therapy, and ligation of the right internal saphenous vein. Other veins involved were the short saphenous, femoral, common iliac, median, basilic, and ulnar. In the interval between admissions the patient continued to have swelling and discomfort in his legs and was thereby prevented from pursuing regularly his duties as clerk. He wore elastic stockings at all times. For 8 weeks at one time he remained in bed under the care of his personal physician for "swelling of the right leg."

From 1939 to 1945 the patient was followed closely in the clinic where he received multiple injections to the veins of the lower extremities.

In July 1945, 2 months after his last clinic visit, he was admitted for the eighth time. He complained of crampy, intermittent epigastric pain which had its onset 4 days prior to admission. Gradually the pain became steady and involved the entire abdomen, being, however, slightly more severe on the right than on the left. Anorexia and nausea were present early but vomiting occurred only on the day preceding admission. Bowels had moved regularly until the onset of pain. Enemata on each of the 4 days before admission had produced light tan stools with no gross blood. There had been no previous gastro-intestinal, genito-urinary, or cardiorespiratory symptom.

Physical examination revealed general abdominal tenderness, worst in the left lower quadrant. A slight resistance to palpation was present over the entire abdomen. A mass, thought to be the descending colon, was felt in the left abdomen. Peristalsis was diminished. Temperature was 100, WBC 13,000 (75 per cent neutrophiles), urinalysis negative. Roentgenograms of the abdomen showed some "gas filled, but not distended, loops of intestine on both sides of the abdomen . . . no more than usually seen." Barium enema one day later yielded no abnormal findings. Forty-eight hours after admission there was a slight distension with spasm and acute tenderness, direct and rebound, localized in the left lower quadrant, where a tender mass could be felt. Diverticular abscess was considered the most likely diagnosis.

On the morning of the fourth hospital day signs of shock appeared and there was blood in the fluids obtained from the stomach by constant suction. The WBC was 29,400 with 86 per cent neutrophiles. Roentgenograms of the abdomen showed increased density but no fluid levels and no free air. Preoperative diagnosis was peritonitis with possible left lower quadrant abscess from a bowel perforation. One observer felt that mesenteric thrombosis was present.

Operation. At celiotomy, when the peritoneal cavity was opened, sanguineous fluid gushed out as tension was relieved. A dark purple loop of jejunum presented in the wound. This loop measured 5 cm. in diameter and shaded from dark purple to normal pink both cephalad and caudad. No internal hernial ring could be found. The process was considered a mesenteric thrombosis. From a point 22 cm. beyond the ligament of Treitz 184 cm. of jejunum was resected and end-to-end anastomosis performed.

Pathology. The specimen consisted of 184 cm. of dark small intestine with an average diameter of 4 cm. It was odorless, without luster, and edematous. Ten centimeters at each end were cyanotic and the central segment was black. The mesentery was edematous and exhibited thrombosis of vessels. Thickness of the intestinal wall averaged 4 mm. in the cyanotic portions and 6 mm. in the black segments. There was a sharp line of demarcation between cyanotic and black areas. Numerous irregular ulcerations were evident in the black section. The lumen contained thick, dark, hemorrhagic material.

Microscopic study of the mesentery showed the veins to be filled with recent thrombi. There was no evidence of perivascular inflammatory infiltration, but there was evidence of recent fibroblastic proliferation. Numerous hemorrhagic areas were seen in the mesenteric fat.

Section of the black zone of the intestine showed gangrene. There was degeneration of the cells in all layers. The mucosal remnants were covered by a thick blanket of amorphous eosinophilic material, blood, inflammatory cells and blood pigment. All tissues showed edema, hemorrhage and recent thrombi in all veins.

Sections from both ends of the specimen showed edema and engorgement of the blood vessels, but nothing else of note. Diagnosis of venous mesenteric thrombosis was made.

Course. The postoperative period was marked by severe abdominal distension for 10 days and a sustained temperature of 102 to 104 for 4 days with a single sharp rise to 105. Two weeks after operation the patient's course became smoother and on the twenty-sixth day after operation he was discharged.

During the next 2 years the patient was followed carefully in the clinic, and one roentgen ray examination showed ". . . no evidence of filling defect, delay or obstruction at the site of the recent jejunal resection." He remained in good health until 1948, 3 years later.

Re-admission. He was re-admitted on March 22, 1948, at 8:00 A.M. with a history of mid-epigastric crampy pain one week earlier and of 3 days' duration with spontaneous remission. While at work as post office clerk during the night, 6 hours before admission, the patient noticed the onset of intermittent crampy pain most severe at a point to the right of the umbilicus. He had no nausea or vomiting but the pain was severe enough to cause him to "double over." He had a "normal bowel movement" 8 hours and a brown fluid stool 4 hours before admission.

At the time he was first seen examination revealed tenderness in the right upper quadrant with minimal rebound tenderness. There was no spasm. Peristalsis was diminished. No mass was outlined . . . WBC was 12,500 with 82 per cent neutrophiles. Four-position films of the abdomen were not contributory.

to 12,500 with 82 per cent neutrophiles. Decision to operate came with the diagnosis of either acute appendicitis or mesenteric thrombosis.

Operation. Thirty hours after admission celiotomy was performed under ether-gas-oxygen-cyclopropane anesthesia with morphine and scopolamine premedication and curare to aid in muscle relaxation. The abdomen was entered through a right mid-rectus incision. Approximately 500 cc. of blood-tinged fluid were aspirated from the peritoneal cavity. This fluid appeared to have been under pressure. Inspection of the small bowel revealed a dark red thickened loop of ileum which showed several small areas of early gangrene in its wall on the mesenteric border. This loop measured 20 cm. in length and lay about 40 cm. from the ileocecal junction. Further examination revealed dark thrombotic areas in the mesentery of this loop. The entire length of small bowel was inspected, but no other disease of the bowel was found. There was nothing remarkable about the previous site of resection. Sixty centimeters of ileum were resected and end-to-end anastomosis accomplished.

Pathology. The surgical specimen consisted of a loop of ileum 60 cm. long with a fringe of mesentery which varied from 1.5 to 2.5 cm. in width. The bowel wall was mottled grey-green to a very dark red, with only small spots of nearly normal color remaining. Microscopic sections of the part of the bowel which appeared involved by the process showed mucosa almost completely destroyed, with marked infiltration by polymorphonuclear leukocytes into the lamina propria. In the more severely damaged portion, the surface was made up of a mass of necrotic cells. There had been much hemorrhage into the submucosa and into the muscularis with infiltration by leukocytes. All blood vessels throughout the bowel wall and mesentery were engorged, the veins showing recent thrombus formation. A section through the bowel immediately proximal to the distal line of resection showed slight engorgement of blood vessels in the submucosa, one vein exhibiting early thrombus formation. The bowel wall was not otherwise unusual. Sections through the normal appearing proximal portion were not unusual.

Diagnosis. Phlebothrombosis, multiple, mesenteric. Gangrene, ileum.

Course. The postoperative course was uneventful. On the first postoperative day the patient was started on Dicumarol medication which was controlled with prothrombin levels. He was discharged on the twenty-ninth postoperative day.

For 29 months he has been on continued Dicumarol medication controlled by prothrombin time determination done twice each week. He is working and asymptomatic.

Case 2.—L. W., 549034, was a female, age 30. Forty hours prior to admission the patient was awakened by severe epigastric colic. All food taken was vomited. On the day before admission she took a "vegetable laxative" and castor oil. She had 20 fluid bowel movements which, she stated, contained no blood. In the months preceding hospitalization she had received arsphenamine and bismuth for secondary lues. A bismuth series was being administered at the time of onset of her abdominal pain, but this was thought to be entirely coincidental.

On admission her temperature was 100.2, pulse regular, and blood pressure 108/78. She displayed a dermatitis resembling pityriasis rosea. Her abdomen was slightly distended, but presented no mass, spasm, or costovertebral tenderness. Peristalsis was present but diminished. WBC was 11,000 with 81 per cent neutrophiles. Urinalysis was unremarkable. Gynecologic pathology was considered improbable by the consultant. An impression of gastro-enteritis was entertained. Three-position roentgen ray films of the abdomen showed only a small amount of gas over fluid levels in the small intestine. Twenty-four hours after admission she suddenly developed shock.

Operation. Transfusion, infusions, and adrenal cortical extracts were given, and under ether anesthesia celiotomy was performed. The peritoneal cavity contained a large amount of blood-stained fluid. Nearly all of the small intestine was purplish-black, had lost its luster, and had no peristalsis. The intestine contained much fluid, later found to be blood, and edema of the mesentery was severe. Fifteen feet of intestine were resected to include all the involved portion. Wherever the mesentery was divided the arteries were patent, but the veins were filled with thrombi which could be extruded

in vermiform masses from small and large vessels alike. It was not possible to resect proximal to the thrombosis at the root of the mesentery. No cause for the thrombosis was found. Anastomosis was accomplished over a Murphy button and the abdomen closed over a drain to the peritoneal cavity.

Pathology. Microscopic study of the specimen showed edema, hemorrhage, necrosis, debris, fibrin, and hemosiderin pigment with polymorphonuclear leukocytes everywhere in the gangrenous areas. Thrombi in the veins of intestine and mesentery were striking.

Course. The surgery, with repeated transfusions, infusions, and other supportive measures, failed to forestall death, which came on the day following operation. No postmortem examination could be done.

Case 3.—W. H., 339700, was a male, age 39. He was admitted complaining of left lower abdominal colic which he had endured for one week. Past and family histories were not contributory. Two days prior to admission the patient took a laxative and had 5 copious passages. On the day prior to admission an enema gave return of brownish fluid thought by the patient to contain blood. Otherwise the patient had passed nothing but flatus for one week. Vomiting had been frequent in the 2 days before admission.

Upon admission temperature was 100.4, pulse 86, respirations 20, and blood pressure 170/95. The undernourished young man was more comfortable in the sitting position and appeared quite ill. The abdomen was distended. Peristalsis was absent. No masses were felt. Tenderness was generalized. Rebound tenderness was present and more marked on the left. Acute appendicitis or diverticulitis or carcinoma of the descending colon with peritonitis were considered.

Proctoscopy revealed nothing, but with the passage of much flatus the patient was relieved of symptoms and distension. WBC was 25,000 with 90 per cent neutrophiles. RBC was 4.8 million and hemoglobin was 12 Gm. Urinalysis showed glucose + + +. Stools and vomitus were guaiaced positive.

Operation. Sixteen hours after admission signs of acute abdominal process continued, and celiotomy was performed under spinal anesthesia. Clear amber fluid was found in the peritoneal cavity. Ninety centimeters of mid-ileum were gangrenous. Resection of 123 cm. was completed and end-to-end anastomosis done. Jejunostomy was performed through a separate incision.

Pathology. The surgical specimen consisted of 123 cm. of small intestine with attached mesentery. At each end of the specimen there was gradual transition from dark brown to more normal color. Everywhere edema was marked; the mesentery measured 0.5 to 1.5 cm. in thickness. The infarcted intestine wall was thinned to 0.3 cm., while the more normal, but edematous, wall measured 0.7 cm. No perforation was present. Microscopic examination showed much of the mucosa to be absent, and in areas where it remained the cell outlines were indistinct. The connective tissue was edematous and gave evidence of erythrocyte diapedesis. Small thrombi were present in venules. Polymorphonuclear infiltration was scattered but prominent. Arterioles and arteries were uninvolved.

Course. The patient developed irreversible shock at operation and died 36 hours later. Postmortem examination revealed the entire superior mesenteric vein and its tributaries to be occluded by a friable and slightly adherent thrombus. Edema of the small intestine nearly occluded the lumen at the site of anastomosis. An older, organized thrombus only partially occluded the inferior vena cava. The deeper portions of this thrombus contained calcium.

Case 4.—R. L., 660903, was a female, age 74. For the 24 hours preceding admission the patient had suffered general abdominal pain and marked abdominal distension associated with passage of gross blood by rectum. "Phlebitis of the legs" had been troublesome "for some time," and 7 years before admission she had had a cerebral accident.

WBC done by her personal physician prior to admission was 18,000 cells with 90 per cent neutrophiles. Significant positive findings on admission included a temperature

of 100, pulse 120, abdominal distension, lower abdominal tenderness, and blood sugar values of 188 and 160 mg. per 100 cc. Hematocrit was 47.7; plasma proteins 7.2; plasma specific gravity 1.028; urine positive for albumin and glucose. Roentgenogram of the abdomen showed gas-distended loops of the small bowel. A diagnosis of gangrene of the small intestine, possibly vascular in etiology, was made. A Miller-Abbott tube was passed into the stomach and operation undertaken immediately.

Operation. With local anesthesia and nitrous oxide supplement the peritoneal cavity was opened in the midline of the lower abdomen to reveal a moderate amount of free sanguineous fluid and 112 cm. of infarcted lower ileum. The mesentery was dark, friable, edematous, and contained thromboses. Resection of 174 cm. was accomplished. Sutures would not hold in the friable intestine at the line of resection. The patient's condition was precarious; therefore a Rankin clamp was applied, a catheter inserted into the proximal bowel, and the abdomen closed, leaving the resected ends of the bowel exteriorized.

Course. The patient's temperature rose to 105° and she died on the third day following operation despite a well maintained blood pressure. Permission for a postmortem examination was not granted.

Pathology. There were 25 cm. and 34 cm. normal margins of intestine at either end of the 112 cm. of infarcted length. Gross blood was present in the intestine. Microscopic examination revealed absence of mucosa and extensive necrosis of all layers, especially of submucosa and muscularis where not even the nuclei of the neurolemma were seen. The hemorrhagic and normal sections both were edematous. Everywhere the vessels were enlarged and the veins in the mesentery of the gangrenous and hemorrhagic region were filled with fresh and some organized thrombi. Arteries were normal.

Case 5.—A. T., 62357, was a female, age 58, who sought medical relief for palpitation, dyspnea, and precordial pain of 2 weeks' duration. She had had slight ankle edema for 3 months. There was no history of previous cardiac difficulties or of rheumatic fever. Nausea was present, but vomiting had never occurred. The precordial pain radiated to the epigastrium and through to the back. At the time ankle edema appeared the patient's personal physician had prescribed digitalis, which had been taken intermittently. During the 2 weeks immediately preceding her admission, the patient had received one or two injections of morphia from her physician for relief of the pain she experienced.

Physical examination showed temperature 101.2, pulse 120, respirations 28, blood pressure 135/55. The patient was well nourished, well developed, had flushed cheeks, and exhibited cyanosis of her nailbeds with clubbing of her fingertips. Her heart was enlarged; its sounds were totally irregular; its impulse was diffuse; a blowing systolic murmur was present at the mitral area. Pretibial and sacral edema were moderate. The isthmus and lower right lobe of the thyroid were enlarged, soft, and possessed a bruit. There was slight dullness at the right posterior lung base.

Laboratory findings were RBC 5.1 million; hemoglobin 12 Gm.; WBC 11,700 with 66 per cent neutrophiles; a stool specimen was negative for blood; urinalysis was not remarkable.

The patient was in the hospital 2 days, during which time she became rapidly worse. The abdominal pain became more severe and was only temporarily relieved by morphine. She was given a soap-suds enema without result. Her pulse remained totally irregular but was of fairly good quality. She died suddenly on the morning of the third day. The clinical diagnosis was cardiac failure with auricular fibrillation.

Necropsy revealed 250 cc. of dark, bloody fluid in the peritoneal cavity. About 2 meters of mid-ileum was a deep red-purple. The transition between normal and abnormal intestine was gradual at the proximal portion but abrupt at the distal. The lumen of the involved intestine contained blood without exudate. Above the involved portion the intestine was slightly dilated and filled with fecal material. The area of discoloration

extended to the base of the mesentery. The trunk and branches of the superior mesenteric artery supplying the involved and uninvolved areas were patent and exhibited no pathologic changes. The mesenteric vein tributaries contained clotted blood. As the portal vein was approached, the clot became more dense. Beneath the pancreas the thrombus was adherent to the intima. The entrance of the splenic vein was occluded, and beyond this point the thrombus tapered in diameter to enter the liver by the right branch of the portal vein. The pancreas was normal. Outline of the involved ileum was retained, but erythrocytes replaced the normal cellular structure.

In summary, there was thrombosis of the superior mesenteric vein with infarction of small intestine. The thrombus appeared to be of some duration—possibly 2 weeks. Platelet thrombi in the pulmonary artery were covered by endothelium. It was impossible to tell whether these arose in situ or were transplanted from the liver via hepatic veins.

A final diagnosis was made of chronic myocarditis, cardiac insufficiency, cardiac arrhythmia, auricular fibrillation, ascites, thrombosis of the superior mesenteric vein, infarction of small intestine, and non-toxic nodular goiter.

Case 6.—S. B., 287914, was a male, age 36, with rheumatic heart disease, auricular fibrillation, and mitral stenosis. He had attacks of severe abdominal pains twice in the 2 months preceding admission. One was accompanied by vomiting, but both receded within one week under conservative sedation and bed rest in other hospitals. Eight days prior to admission he suffered onset of a third episode of similar generalized abdominal pain and vomiting.

Upon admission his temperature was 101.4, pulse 76, respirations 20, and blood pressure 150/90. He squirmed in pain and begged for relief. In addition to a mitral rumble on cardiac auscultation he revealed direct tenderness and voluntary spasm over the lower mid-abdomen without distension or masses. WBC was 24,100 with 91 per cent neutrophiles, hemoglobin was 16 Gm., RBC was 7.5 million, urinalysis normal. Roentgenogram of abdomen revealed no pathologic condition. A diagnosis of embolism of the mesenteric artery was made and exploration of the abdomen undertaken with spinal anesthesia supplemented by nitrous oxide.

Operation. A moderate amount of thin, apparently non-infected, serosanguineous fluid was present in the peritoneal cavity. A 20 cm. loop of small intestine in the left lower quadrant was dark red, edematous, and rigid. The mesentery of the involved loop was edematous, injected, and contained several blood clots. Fifty-five centimeters of small intestine were resected with a wedge of mesentery and end-to-end anastomosis done. A catheter enterostomy was placed above the anastomosis.

Pathology. Microscopic examination showed degeneration of the superficial mucosa, infiltration by leukocytes of all bowel layers, and hemorrhage everywhere. Sections through the mesentery showed thrombosis of veins with beginning organization. Careful search uncovered no thrombosis of any artery.

Course. The patient's condition rapidly deteriorated and he died a few hours after operation. Necropsy was not permitted.

Case 7.—J. D., 934607, was a female, age 73. Previously always well and active, the patient had had a complete physical examination by her personal physician 2 weeks prior to her hospital admission. Three pregnancies and deliveries in earlier years had been uncomplicated.

About a week before admission she began to have a heavy feeling in the lower chest when eating and vague abdominal discomfort with flatus and looseness of bowels. This continued until the morning of admission, when she felt generally upset and called her physician. He found normal temperature and pulse and a blood pressure of 150/90. In the afternoon generalized abdominal cramps, nausea, and vomiting began. In the early evening she stated that the pain was severe and localizing in the right lower quadrant.

Upon her admission temperature was 98.2, pulse 86, and blood pressure 150/90, and she was somewhat dehydrated. Her abdomen was soft, flat, tender in both lower quadrants with rebound tenderness in the left lower quadrant. Costovertebral angles were negative. In 3 hours the tenderness localized at the outer border of the rectus on the right side just below the umbilicus, where there was spasm. Hemoglobin was 15.8 Gm., RBC 5.2 million, WBC 13,400 with 85 per cent neutrophiles. Urinalysis showed a slight albuminuria and glycosuria. An impression of acute appendicitis was held and exploratory laparotomy undertaken immediately with Pentothal, cyclopropane anesthesia with curare for added relaxation. One thousand cubic centimeters of 5 per cent dextrose in saline and 1000 cc. of 5 per cent dextrose in distilled water were given.

Operation. The abdomen contained a moderate amount of clear blood stained fluid. The appendix was normal. In the upper portion of the ileum a segment 23 cm. in length was edematous and deep violet-red in color. The mesentery of this loop was thick, edematous, and filled with well-formed thrombi. There was no bleeding from the arteries in the mesentery immediately underlying the lesion, but there was free bleeding from the arteries in the more outlying areas where veins contained thrombi. It was presumed, therefore, that this was a venous thrombosis. The appendix was normal but was removed. Forty centimeters of ileum were resected so as to leave a wide margin of good intestine on either side of the damaged area. When the resection was completed there was free bleeding of bright red blood from all the cut surfaces. Anastomosis was made in a double layer, and the wound closed with difficulty because the tissues were friable. A drain was left in the subcutaneous tissues.

Pathology. Microscopy showed the large veins of the mesentery to be densely packed with erythrocytes, among which ran many strands and sheets of fibrin containing many polymorphonuclear cells and platelets. An artery was distended with blood but contained no thrombus. Edema and fibrin network were present in all the layers of the intestine. There was superficial denudation of some areas of mucosa.

Course. Twelve hours after the operation the venous clotting time was 17 minutes. Twenty hours after operation heparinization was begun. The clotting time as taken just before the three hourly dose of heparin was maintained at an average time of 17 minutes for 11 days. Recovery was without event except for a slight serosanguineous drainage from the wound which suggested deep-layer disruption. The patient was discharged from the hospital on the seventeenth day after operation. Ten months later she was well and active with an asymptomatic small incisional hernia which required no treatment. Her prothrombin time was 12.5 seconds (normal value 14 seconds with plus or minus 2 deviation), and her clotting time was 5 minutes.

Case 8.—D. S., 804329, was a male, age 73. His history follows:

1935. Intermittent, undiagnosed abdominal pain. Acute pyelitis after diagnostic cystoscopy.

1937. Right upper quadrant pain. Toxic nodular goiter. Operation was delayed 2 months while investigation of possible bronchiectasis was concluded.

1938. Partial thyroidectomy.

1945. October to November—Arteriosclerotic heart disease with bilateral pleural effusion, early congestive failure, and pulmonary infarcts, cause unknown.

One month after going to a convalescent home the patient was re-admitted. He complained of epigastric cramps associated with dyspnea, orthopnea, and vomiting. Fever of low degree had persisted for two days.

On admission his temperature was 102.6, pulse 100, respirations 32, and blood pressure 128/65. Hemoglobin was 13 Gm., RBC 5.2 million, WBC 10,600 with 82 per cent neutrophiles. Urinalysis showed a moderate amount of albumin and rare formed elements. The WBC climbed to 14,700, and the abdomen became distended and generally tender but never evinced spasm or mass. Stools were guaiac positive; vomitus

was negative. Death came on the fourth hospital day despite penicillin therapy for right lower lobe pneumonia.

Postmortem examination showed generalized arteriosclerosis including the arteries of the mesentery. Healed cardiac infarcts were evident. Calcific stenosis of the aortic valves was present. Superior mesenteric vein thrombosis with focal infarction of the small intestine, right colon, and spleen was an unsuspected finding. Microscopy displayed the arterial intima and media to be moderately thickened and the lumen to be partially obliterated by connective tissue. The veins contained large masses of recent thrombus completely occluding the vessels. Autolysis did not obscure the usual architecture of focally infarcted intestine.

Case 9.—R. H., 361340, was a male, age 43. Two weeks of severe epigastric "cramps," constipation, and a low grade fever brought him to the hospital. He had had 8 episodes of epigastric "cramps" in the preceding 2 years, but they had all been relieved by enemata. Past history was otherwise not contributory. He had never had an operation.

The pains leading to his hospitalization were preceded by a half-day of headache, drowsiness, and inability to concentrate. For his cramps the patient ingested Seidlitz powders without relief. An enema gave some comfort but the cramps continued. After a night with fever of 102° and delirium he called his personal physician, who gave him codeine. The cramps subsided, leaving a dull steady pain in the lower abdomen and in the right upper quadrant. Much flatus was passed. Fever continued unabated. There was no nausea or vomiting though anorexia increased.

Upon admission he was found to have a temperature of 103.6 and a pulse of 96. WBC was 26,800 with 90 per cent neutrophiles. Blood culture proved negative. Stools revealed no parasites or occult blood. Cystoscopy was not remarkable, although urine was seen to contain bile. Roentgenograms of chest, abdomen, and liver area gave no aid. Liver abscess was suspected. Icterus index was 12.5, but plasma bilirubin was 2 mg. per 100 cc. Agglutination for brucellosis was negative.

On the sixth day after admission he had profuse watery diarrhea and recurrence of severe epigastric cramps. The seventh day saw the onset of tenderness, direct and rebound, in both lower quadrants. Liver percussion elicited no pain. Diagnosis of an acute abdominal situation led to exploratory celiotomy with ether anesthesia.

Operation. An unsuspected extensive thrombosis of the superior mesenteric vein and portal vein was discovered. The thrombosis was firm and not suppurative. Ligation of the portal vein was thought to be a hopeless procedure. No evidence for liver abscess was made out. The appendix appeared normal, but appendicectomy was done with a terminal ileostomy.

Pathology. The appendix was a small, white, non-injected, shriveled organ measuring 2.2 by 0.7 cm. The wall was fibrous. Microscopy showed some necrotic material in a tiny lumen at the proximal portion. Tissues were well preserved with a diffuse scattering of polymorphonuclear leukocytes. Lymphatics and blood vessels were dilated, and one venule appeared thrombosed. The pathologist felt that the histology probably represented an inflammatory process in the whole of the intestinal tract involved by the mesenteric occlusion.

Course. On the second day after the operation the patient died; necropsy was not performed.

Case 10.—C. E., 967794, was a female, age 52. Fifteen days prior to admission, after 2 or 3 months of poor appetite with watery eructations and a weight loss of 10 to 20 pounds, the patient suffered onset of a low grade fever, distension, and diffuse pain in the abdomen—worse in the left lower quadrant. During the 4 days immediately preceding admission she had, in addition, severe crampy pain in the entire right side and mid-back. Bowels had always moved irregularly. There had been no evident gastrointestinal bleeding. Though anorexia was prominent vomiting had not occurred.

Five years ago the patient had diarrhea and parasites in the stools for which she received treatment. One year before the present admission stool examinations revealed no parasites or ova. Three months ago, shortly before onset of the present illness, she experienced an acute episode of malaria proved in blood films and treated successfully with Atabrine and quinine. Cystitis had been an occasional mild irritation for several years. Menses continued normally, and the most recent had been completed just before the present hospitalization.

Physical examination demonstrated the significant findings of diffuse abdominal tenderness more severe in the left lower quadrant. No spasm was present. Some rebound tenderness could be elicited. The costovertebral angle was only slightly tender on the left. Temperature was 98.8, pulse 86, respirations 20, and blood pressure 110/50.

Hemoglobin was 8.0 Gm., RBC 3.4 million, WBC 8400 with 70 per cent neutrophiles. Urinalysis revealed nothing unusual. Serum amylase was 32 Myers and Killian units—within the normal range. A roentgenogram of the abdomen demonstrated no gas or pathology.

The patient complained that her abdomen felt as though it were distending and she was restless and perspired a great deal. Demerol and barbiturates failed to give complete surcease from her abdominal pain. Erythrocyte sedimentation was elevated to 62 mm./hr. Serum bilirubin was 0.5 mg. per 100 cc. The first stool specimen was negative for occult blood, parasites, and ova; the second gave a positive guaiac test. Sigmoidoscopy gave no added information. Priodax given for gallbladder examination remained in the stomach 18 hours. Barium enema suggested possible diverticulitis. WBC rose to 17,500 with 86 per cent neutrophiles. Hemoglobin dropped to 6.5 Gm. with parenteral fluid infusion. Temperature rose to 100.2. Sulfadiazine and penicillin therapy were instituted. Sulfadiazine was soon discontinued when urinary output began to fall, although there was no hematuria or other evidence of nephritis. Dehydration was combated with increased amounts of parenteral fluid. Morphine replaced Demerol, but still not all pain was relieved. Symptoms vacillated in severity. Streptomycin therapy was begun.

Gross blood was passed per rectum and vomiting began. The vomitus was of fecal odor and without blood, and measured 2000 cc. in two days. A Miller-Abbott tube would not pass through the stomach. The surgical consultant observed the patient to be dehydrated and with a rotund, distended, tender abdomen; there was no spasm, scar, or mass, and direct and rebound tenderness was referred to the left lower quadrant where there appeared a soft mass hours later. Audible peristalsis was very occasionally present. Slight rectal tenderness was without localization and there was no fullness of the Pouch of Douglas.

NPN was 33. CO_2 was 53 vol. per 100 (28 meq/l) and serum chlorides 519 mg. per 100 cc. (89 meq/l). Repeat roentgenograms of the abdomen revealed nothing unusual; her GI series suggested a partial obstruction of small intestine. It was decided that signs of peritoneal irritation were clear and the most likely possibility seemed to be some complication of diverticulitis.

Operation. Therefore, 8 days after admission celiotomy was performed under ether-cyclopropane anesthesia. One liter of clear amber fluid was in the peritoneal cavity. In the left lower quadrant was a purple-red loop of jejunum with thickened wall and 4 cm. diameter; there was very little fibrinous exudate and the serosal surface glistened. The loop was adherent to adjacent omentum and to descending colon. When these adhesions were divided, blood oozed freely. Two neighboring segments of jejunum about 12 cm. in length were involved with 15 cm. of more normal appearing bowel between. The mesentery was 1.5 cm. thick, hard, and inflexible. When cut, the vessels of the mesentery permitted extrusion of stringy, gelatinous casts from small vessels. Resection was accomplished with end-to-end anastomosis about 4 feet distal to the ligament of Treitz.

Pathology. The resected jejunum measured 51 cm. in total length. The mucosa was thickened and hemorrhagic. Microscopic sections showed mucosal ulceration and the submucosa was infiltrated diffusely with lymphocytes and neutrophiles. Eosinophiles were not prominent. Many thrombosed veins showed early fibroplastic organization with some recanalization. Recent thrombi were also present in the veins. Sections through the mesentery revealed the arteries to be everywhere patent and normal, while veins were thrombosed and undergoing organization. The lines of resection were free of disease.

Course. 3000 cc. of whole blood were given in the days before, during, and after the operation. Hemoglobin rose to 11.6 Gm. and RBC to 4 million with a hematocrit of 34.6. Temperature rose to 101.6, pulse to 100. Dyspnea with cyanosis occurred suddenly on the sixth postoperative day. Roentgen ray evidence suggested infarct of bronchopneumonia. There was no evidence for extra-abdominal sites of thrombosis. Heparinization was accomplished. A pleural friction rub appeared and the patient was placed in an oxygen tent. The WBC was 20,300 with 87 per cent neutrophiles. Gradually the WBC dropped and the patient improved. Cephalin flocculation, thymol turbidity, alkaline phosphatase determinations were within normal range. Studies for parasites in the stool were repeatedly negative.

On the fiftieth hospital day, 42 days after operation, the patient left the hospital with no disability. Clotting time was 8 minutes. Platelet count showed 270,000 platelets. Prothrombin time was 20.2 seconds (normal 16 ± 2 seconds). Total plasma proteins were 7.21 Gm. per cent. Protamine titration was within normal range.

Case 11.—A. R., 53967-48 (BH), was a male, age 40. The patient was admitted to Bellevue Hospital with a history of severe, colicky, generalized abdominal pain of 11 hours' duration. This pain had been preceded by 5 days of intermittent, vague, mild abdominal cramps with no accompanying difficulty. Diarrhea and vomiting had not occurred. Physical examination demonstrated direct and rebound tenderness referred to the entire abdomen but more severe in the right lower quadrant.

Previous illnesses had included appendicitis with appendicectomy at the age of 5 years. Viral parotitis occurred when the patient was 35 years of age. During the period of 14 years preceding this admission, there were 3 hospital admissions for thrombophlebitis of the lower extremities and home treatment of several minor thrombotic episodes in the leg veins. Evidence of pulmonary infarction was prominent during the first hospital admission. There was no history of any other disease, operation, or injury.

Family history as corroborated by records from other hospitals revealed the patient to have been one of four brothers, two of whom had had intestinal resection for venous mesenteric thrombosis.

One brother, at the age of 36 years, underwent appendicectomy in January, 1934, at a New York hospital. The postoperative course was complicated by pneumonia and bilateral thrombophlebitis of the lower extremities. He was convalescing—still in bed—2 months later in March when he began to experience indigestion, anorexia, nausea, vomiting, and pain in the lower abdomen. Physical examination revealed the abdomen to be distended. Periumbilical pain and tenderness were striking. There was no rigidity, and no masses were felt. Hemoglobin was 64 per 100 cc., RBC 3.8, and WBC 12,800. At operation in April, 1934, two and one-half months after the appendicectomy, venous mesenteric thrombosis with gangrene of the ileum were found. Resection of two and a half feet of ileum with end-to-end anastomosis of small intestine was performed. Histologic examination was interpreted as showing thrombi in veins, edema and hemorrhage into the wall of the ileum, and no arterial lesion. Following surgery there was some distension, but this gradually subsided, and at the time of discharge on the thirty-sixth postoperative day the intestinal tract was functioning normally. Fear of recurrence has induced this patient to ingest Dicumarol without medical supervision. He has had three large gastrointestinal hemorrhages treated in three hospitals in various parts of the United States.

The second brother, an M.D., was admitted in 1939 to another New York hospital with acute colicky abdominal pain. This brother told the hospital physicians that he believed the diagnosis to be venous mesenteric thrombosis since he had had venous thrombi in his leg a short time before and because his 3 brothers were subject to intravascular thrombosis or thrombophlebitis. Some time before this admission he had been hospitalized with spontaneous left leg phlebitis complicated by pulmonary infarction. At this admission for abdominal pain he looked very ill, was pallid, and had cyanotic lips. His pulse was of poor quality. His abdomen was uniformly distended and tense with slight tympany on the right side. Peristalsis was absent. Intraperitoneal fluid could not be detected. Tenderness was marked over the left upper quadrant. Hemoglobin was 108 per cent, RBC 5.6 million, WBC 24,100 with 85 per cent neutrophiles. Wassermann was negative. Urine contained albumin and reduced Benedict's reagent. Blood urea nitrogen was 20, and blood sugar was 266. Roentgen ray examination of the abdomen showed gaseous distension of stomach, distal small intestine, and right half of the colon. Barium enema examination gave no significant positive information. It was decided that operation could not be undertaken with the patient in so poor a condition. A Miller-Abbott tube was inserted but did not pass beyond the duodenum. Two days after admission he passed gross blood per rectum and vomited blood containing material. Operative exploration of the abdomen was done through a left rectus incision. A large quantity of brownish, non-odorous fluid was found free in the peritoneal cavity. Cultures were taken and the fluid was removed by suction. The presenting small intestine except for the terminal ileum was purple-red but the overlying peritoneum was glistening. The entire small intestine except for the terminal ileum was edematous, discolored, and hemorrhagic together with its mesentery. Colon, stomach, liver appeared normal. Because of the extent of disease and the poor condition of the patient no resection was attempted. The abdomen was closed in layers without drainage. Transfusion and other supportive therapy were of no avail and death came on the fourth hospital day. Necropsy revealed the edematous, discolored small intestine. The thickened, congested, hemorrhagic, edematous mesentery contained the tributaries of the superior mesenteric vein which were filled with firm, gray-red, adherent thrombi extending into the portal vein. All the arteries were free of thrombus. One large venous tributary draining a scarred area of renal cortex contained an organized thrombus.

In the face of this family history, the patient, A.R., felt that he, too, had venous mesenteric thrombosis. His temperature was 100; WBC 17,000, clotting time (Lee-White) 2.5 minutes. Physical examination showed a moderately obese male with a well-healed right lower quadrant abdominal scar. There was no abdominal distension, but tenderness was acute and accompanied by rebound phenomena over the entire abdomen and worse in the right lower quadrant. Audible bowel sounds were absent. No masses were palpable. No hernia or costovertebral tenderness was identified. Blood was cross-matched, and 4 hours after admission celiotomy was performed.

Operation. Under spinal and general anesthesia, through a lower right rectus incision about 70 cm. of very dark ileum was identified. Its distal portion was 25 cm. from the ileocecal valve. With the Furness clamp technic the ileum was resected through normal appearing areas and an end-to-end anastomosis was accomplished. Careful examination revealed no other pathologic condition of the intestine.

Pathology. Microscopic examination of the resected intestinal segment revealed an intact mucosa. Moderate edema was present in the entire thickness of the wall. Congestion of subserosal and intramural blood vessels was prominent. Sections through the mesentery exhibited many thrombosed veins. No arterial thrombosis was demonstrated. The walls of the veins showed no inflammatory reaction.

Course. The patient was given 1500 cc. of whole blood during and after the operation. Dicumarol was administered postoperatively. Fifteen days after operation he felt well and was discharged to his home. Eleven months later he was asymptomatic and in good

health with only a weakness in abdominal musculature under the operative scar. At this time he was taking no anticoagulants. Prothrombin time was 16.1 seconds (normal 18 ± 2 seconds); platelet count 220,000; clotting time was ten minutes by the Lee-White method. Protamine titration for heparin sensitivity or circulating heparin-like substance was within normal limits. Total plasma protein was 8 Gm.

Case 12.—D. F., 629258 (P.C.), was a male, age 50. The patient presented himself stating that he had awakened 4 days earlier with a periumbilical pain, dull and intermittent in quality. The pain continued, becoming more severe as time passed. On the third day of his pain he induced vomiting without relief. On the morning of his admission he began to vomit spontaneously and profusely. He vomited a greenish-yellow material 6 or 10 times without relation to or relief of the pain. He had noted no bowel changes, nocturia, or frequency. He was pale, perspiring profusely, and walking about while stating that he was in acute pain. His blood pressure was 110/60. The skin was cold and moist. Examination revealed nothing focally significant. His abdomen was soft, obese, but diffusely tender. A perforated ulcer was suspected. Roentgen ray film of the abdomen showed nothing unusual. He was admitted to the ward. His temperature was 101.2. One-quarter of a grain of morphine failed to relieve the pain, and the patient paced up and down complaining all the while of severe abdominal pain.

Hemoglobin was 14 Gm.; RBC 4.95 million; WBC 18,200 with 76 per cent neutrophiles; plasma proteins 6.6 Gm.; urinalysis 1+ reducing and 1+ protein. Blood sugar was 50 mg. per 100 cc.

The patient was given intravenous fluids, antibiotics, Levin tube with continuous suction and nothing by mouth. On the second hospital day he passed blood in a liquid stool. That evening he passed more blood by rectum. He complained of severe cramps in the right lower quadrant. Blood pressure was 128/84 and pulse was good. Later in the evening he felt better. By the next morning the patient was in shock with thready pulse and blood pressure 60/40.

A consultant felt that the most likely diagnosis was that of bleeding ulcer with perforation. The Levin tube drainage was bloody, and more blood was passed by rectum. With treatment the patient seemed to improve, then became irrational, cyanotic, anuric, and expired on the fourth hospital day without recovering from the shock state.

Necropsy showed a thickened, dark-red, and in some areas gangrenous small intestine from a point 15 cm. distal to the duodenum to a point 7 cm. proximal to the ileocecal valve. The peritoneal cavity and the bowel lumen contained bloody fluid. The superior mesenteric artery was patent throughout its length, but all the tributaries of the superior mesenteric vein were thrombosed. The mesentery was thickened and contained large areas of ecchymosis.

DISCUSSION

Discussion of this material quite naturally follows two pathways. First, there is the consideration of agnogenic venous mesenteric thrombosis and a study of the material presented. Second, the somewhat confused problem of coagulation of the blood will be considered to see if, by study of these factors, we have any means at present which might aid in earlier diagnosis and more effective treatment of this condition.

Agnogenic venous mesenteric thrombosis lacks definite etiology because there is no scientific evidence that any factors, alone or in combination, are responsible for initiation of the process. Four lines of inquiry present themselves:

(a) There may be temporary kinking, volvulus, intussuception, hernia or other temporary obstruction to venous blood flow. Operative findings on

some pure venous mesenteric thromboses have been associated with these obstructions to circulation in the mesentery.

(b) Infection and sepsis may be the underlying cause as with septic pylephlebitis complicating suppurative conditions within the abdomen.

(c) The etiology may be attributed to Banti's disease, cirrhosis of the liver, portal hypertension, or tumors. There is no evidence of any of the above, however, in the true idiopathic variety of mesenteric thrombosis.

(d) In the group of cases we are reporting as agnogenic venous thrombosis it seems most likely that some change in balance of the hematologic elements concerned in coagulation probably plays the major role in producing thrombosis of the mesenteric veins. This dyscrasia is indeed necessary for thrombosis and may be induced by some local damage to the intima and stagnation of the circulation or by other known or unknown factors. Such a temporary imbalance might follow over-transfusion, perhaps, or severe enteritis with fluid loss and resultant hemoconcentration and temporary thrombophilic state. General factors, too, probably have a role, as suggested by the cases reported.

With the increasing use of antibiotics the question has arisen as to whether or not there may be a resultant increase in blood coagulability.[24, 25] At present the evidence is insufficient and unsubstantiated. Certain drugs also, such as the digitalis[26-28] group have thromboplastic properties, and the mercurial diuretics have also been implicated.[29, 30] In addition, the frequency of migratory phlebitis in patients with carcinoma,[31] notably of the pancreas, suggests a change in the clotting mechanism in these conditions. This, perhaps, may be in whole or in part attributed to the anemia that usually accompanies malignant disease.

SYMPTOMS AND SIGNS FOR DIAGNOSIS

Clinical descriptions of venous mesenteric thrombosis have been modified by inclusion of arterial and mixed venous-arterial thromboses, but most of all by addition of the symptoms and signs of those diseases commonly associated with the venous thromboses. Thus appendicitis, hepatic cirrhosis, abdominal neoplasia, adhesions, volvulus, strangulated hernia, salpingitis, and diverticulitis have contributed confusing symptoms and signs to mislead the clinician.

Prodrome. Agnogenic venous mesenteric thrombosis often displays a prodromal period. This may be represented by a past history of "migrating thrombophlebitis," lower extremity "thrombophlebitis," pulmonary infarcts, or vague abdominal discomfort of episodic character. In addition, the prodrome may be characterized by diffuse, intermittent, abdominal pain which is often colicky and may last days or even several weeks.

Acute Symptoms. The more acute symptoms are those of intestinal obstruction or, less commonly and later in the course of the disease, symptoms of peritonitis. In our series all patients complained of abdominal pain (Table III). The pain was intense, often intermittent and colicky, and was general-

ized or with exaggeration in any region of the abdomen. Peculiarly, it possessed an intensity not easily controlled by opiates. Vomiting occurred in more than half of the patients. Hematemesis, a very suggestive though not diagnostic symptom, was rare, occurring in only one case. Blood in the stomach might be expected as a late sign since infarction of the intestine was

TABLE III.—*Presenting Symptoms, Temperature and Pulse.*

Case	History and Presenting Complaint	Temp.	Pulse
1	7 attacks of phlebitis—epigastric pain—colic—vomiting	100	90
1A	Mesenteric thrombosis—epigastric pain—colic—vomiting	99.8	88
2	Epigastric colic—vomiting	100.2	..
3	Abdominal cramps—vomiting	100.4	86
4	Severe abdominal pain—distension	100	120
5	Severe abdominal pain—constipation	101.2	120
6	Abdominal pain—vomiting	101.4	76
7	Abdominal discomfort, then severe pain	98.2	86
8	Abdominal pain	102.6	100
9	Abdominal cramps—constipation	103.6	96
10	Abdominal pain—anorexia	98.8	86
11	Severe abdominal colic	100	..
12	Severe abdominal pain—vomiting	101.2	..

always some distance beyond the ligament of Treitz. Though diarrhea and constipation are described as common findings in series of mesenteric vein occlusion from mixed causes, agnogenic venous thrombosis is not often heralded by bowel irregularities. When the prodromal period was several days in length, constipation was more common.

TABLE IV.—*Presenting Physical Signs.*

	Physical Examination					
Case	Distension	Spasm	Tenderness	Rebound	Mass	Peristalsis
1	+	0	+	0	+	Decrease
1A	0	0	+	+	0	Decrease
2	+	0	+	0	0	0
3	+	+	+	+	0	0
4	+	+	+	0	0	
5	+	0	0	0	0	0
6	0	+	+	+	0	
7	0	+	+	+	0	
8	+	0	+	0	0	0
9	+	0	+	+	0	
10	+	0	+	+	+	Decrease
11	0	+	+	+	0	0
12	0	0	+	+	0	

Physical Signs. In series of mesenteric vein thrombosis with mixed etiology abdominal signs are often confused with those of acute appendicitis or other emergencies (Table IV). Upon admission agnogenic thrombosis presents as a frequent finding a striking disproportion of abdominal rigidity to the probable duration of symptoms and to palpation tenderness in the abdomen. Rigidity is often very slight or entirely absent, although tenderness is acute. Rebound tenderness, usually considered to represent peritoneal inflammation, is not seen in the first days of symptoms. Distension occurs

quickly in most cases but frequently lacks tympanitic qualities because the distended loops of intestine are filled with fluid and blood. When these loops are so filled, roentgenograms fail to show gas-distended intestinal shadows; gas shadows, however, appear in about half the cases and may have a peculiar distribution. According to Harrington[32] a film that shows gas in the proximal half of the colon, stopping abruptly in the mid-transverse colon, is a helpful finding. Free fluid in the peritoneum is always present in amounts usually measuring from one-half to one liter. All observers agree that distension and fluid loss into the peritoneal cavity and intestine are greater in venous mesenteric occlusion than in the arterial form. A palpable loop of intestine is rarely felt because it lies behind a stretched abdominal wall and because palpation elicits tenderness and voluntary guarding sufficient to hide the soft mass of intestine, which with a structurally open lumen everywhere, permits the accumulated fluid in the paralyzed segment to be easily displaced by pressure of the examiner's hand.

TABLE V.—*Laboratory Data.*

Case	HGB (Gm.)	RBC	WBC	Neutrophiles Per cent	Guaiac	Other
1	....	.....	13,000	75	.....	
1A	16.2	.....	12,500	82	F +	
2	9.7	4.1 million	11,000	81	.....	
3	12.8	4.8 million	25,000	90	V 4+ F 4+	
4	11.9	4.2 million	18,000	90	V 3+ F Gross	
5	12.0	5.1 million	11,700	66	F 0	
6	16.0	7.5 million	24,100	91	.....	
7	15.8	5.2 million	13,400	85	Enema 0	
8	13.0	5.2 million	10,600	82	V 0 F 4+	
9	....	3.9 million	26,800	90	F 0	
10	8.0	3.4 million	8,400	70	F 2+	
11	....	.....	17,000	..	.....	Clotting time 2.5 min.
12	14.0	4.95 million	18,200	76	F Gross	

V = vomitus. F = feces.

Melena, gross or occult, occurs less frequently than one might expect from the rather consistent finding of blood in the involved intestine, inasmuch as blood in the small intestine with associated paralytic ileus may not find its way to the large bowel to be identified in stool, gloved-finger specimen, or enema return. About one-third of the patients in this series displayed melena. Increased attempts to demonstrate melena by use of the "diagnostic enema" and guaiac test may increase somewhat the positive findings; when positive, this test is a valuable aid in diagnosis.

Borborygmi may be marked when the intestine demonstrates increased peristalsis, later, as paralytic ileus develops, audible peristalsis is diminished or absent. Vomiting is common as in any intestinal obstruction and guaiac tests on vomitus may be positive for blood.

Shock is rare and is a late and grave sign of venous mesenteric thrombosis. In Whittaker and Pemberton's[11] series, 47 per cent of arterial occlusion and only 7 per cent of venous occlusion demonstrated shock.

Temperature in most early cases is not elevated. After several days of severe symptoms the temperature may rise to between 101 and 103. The pulse varies but rises as time passes. Leukocytosis averages about 20,000, somewhat lower than the 27,000 of arterial occlusion. The average admission WBC for this series was 18,000 with 83 per cent neutrophilic leukocytes (Table V).

At operation the finding of sanguineous fluid in the peritoneal cavity should immediately suggest the possibility of venous mesenteric occlusion. Early the fluid is odorless, but after invasion by organisms penetrating infarcted intestinal wall it develops a foul odor.

Unless the disease is kept in mind for all patients with a suggestive history and physical examination the diagnosis will not be made. Even the

TABLE VI.—*Preoperative Diagnoses in Series Reported.*

Case	Preoperative Diagnoses	Cases	Preoperative Diagnoses
1	Peritonitis	7	Acute appendicitis
1A	Appendicitis, ? mesenteric thrombosis	8*	Lower lobe pneumonia
2	Acute abdomen	9	Acute abdomen, ? liver abscess
3	Acute appendicitis, lesion large bowel, peritonitis	10	Diverticulitis, ? perforation
4	Gangrene small intestine, ? vascular	11	Venous mesenteric thrombosis (diagnosis made by patient)
5*	Cardiac failure, auricular fibrillation	12	Bleeding peptic ulcer, perforation
6	Embolism of mesenteric artery		

* No operation. Necropsy only.

diagnosis, however, is not as important as the recognition by the surgeon of the fact that he is dealing with an acute abdominal emergency which requires immediate intervention. On no account should operation be delayed in order to attempt an academic diagnosis (Table VI).

Only 5 per cent of Trotter's[8] and 15 per cent of Cokkinis' series were correctly diagnosed before operation. That the diagnosis is frequently in error is not surprising in view of the lack of distinguishing findings. Non-specific enteritis, typhoid, cholecystitis, appendicitis, peptic ulcer, volvulus, internal hernia, adhesive bands with obstruction, intussuception, lead poisoning, acute pancreatitis, in fact most acute abdominal emergencies, can be simulated during some stage of the disease. It is important that, despite the frequent lack of spasm and rebound tenderness early in venous mesenteric thrombosis, the condition be recognized as an acute abdominal emergency.

Pathology. Complete occlusion of the superior mesenteric vein or a portion of its tributaries while all arterial branches remain patent constitutes the dominant feature of agnogenic venous mesenteric thrombosis. Associated with the venous thromboses in those cases that come to surgery or postmortem examination are severe structural changes in intestine and mesentery. With etiology yet to be determined it is impossible to ascribe initiation of the patho-

logic process to any portion of the structural pattern. It seems reasonable, however, that whatever the cause of preceding events, thrombosis of the venous channels represents a stage in pathogenesis to which the other observed functional and structural pathology can be attributed. The patterns of the lesions vary with the degree of vascular occlusion and with the age of the lesions.

An uninfected thrombus recently formed in a vein is dark-red, gelatinous, easily withdrawn from the lumen, and unattached to intima. With the passing days the thrombus becomes grey, firm, and adherent to the intima as fibroblasts invade to organize the mass. Various stages of this process present simultaneously, thereby suggesting that thrombosis has occurred intermittently or progressively and may have blocked anastomosing channels until collateral circulation is impossible. One-fourth of the cases with surgical resection exhibited organized as well as more recently formed thrombi. The extent of thrombosis varies within wide limits and may even include the portal, splenic, and tributaries of the superior mesenteric vein, even to the intramural vessels. Whether thrombosis begins in the finer tributaries or in the larger collecting veins cannot be determined from the limited amount of material so far available. If the segments of diseased intestine in this small series could be considered a reasonable indication, it would appear that thrombosis of the ileal veins is about twice as frequent as thrombosis of jejunal veins.

Edema and extravasation of blood into the mesentery produce a thickening which often measures 2 to 5 cm.; this often obscures all pulsations and architecture in the mesentery. Various lengths of small intestine, in this series from 18 to 250 cm., present as dark-red, purple, or blue-black loops. Gross perforation was not present in this group but may conceivably be a late complication. The walls of the intestine are usually much thickened by infiltrations of blood and plasma but the serous coat retains a gloss that is only infrequently broken by flecks of fibrin. Especially in cases with long-existing symptoms there may be adhesions with omentum or other loops of intestine. These adhesions carry patent blood vessels and probably act as collateral channels. In a case of acute pancreatitis with associated venous mesenteric thrombosis, but not included in the present series, anastomoses of ileal veins with the right ovarian vein were found patent and measuring 0.5 to 1.0 mm. in diameter. Also, in Case 10, adhesions of the involved small intestine to omentum and descending colon exhibited free bleeding when divided.

TREATMENT

The treatment of this abdominal catastrophe is *operative*. As with acute intestinal obstruction, the time for surgery is before one's hand is forced. The presence of an acute abdominal emergency should be recognized and the temptation to delay until the perfect diagnosis can be established must be

eschewed. In studying our series of cases one cannot but be somewhat appalled at the long delays between admission to the hospital and decision to operate. Today, exploratory celiotomy, even in the aged, carries little risk—one far lower than when operation is too long delayed in intestinal obstruction, whatever its cause. And when there is the added risk of a progressing thrombosis, the urgency of surgery is still more clearly indicated.

Prior to the advent of the anticoagulants the operative mortality was so high that some advocated expectant treatment. A fallacy in this advice is the very great question of accurate diagnosis in the non-operative group. In the group reported, for example, only two correct diagnoses were made, in one instance by the patient. There can be little sound argument, therefore, for expectant treatment; in fact it seems likely that with this form of therapy the mortality will be over 70 per cent.[9, 33] The surgical mortality figures for the series reported in the past are likewise high but no differentiation has been made between arterial and venous thrombosis. In our own small group of 13 cases of the agnogenic venous variety there were eight deaths. After reviewing some of the literature and studying our own series it is probable that the mortality might well have been lowered by earlier operation.

As has been stated already there were two deaths in Murray's[12] group of six cases treated with resection and heparin. One was from bronchopneumonia and one from peritonitis. Necropsy showed no extension of the thrombosis in either instance. An increasing number of cases treated successfully with heparin has been reported during the past decade, and in our series all but one of the patients who recovered were so treated.

In essence, then, a successful outcome depends upon early operation with resection of the involved area and prompt institution of anticoagulant therapy postoperatively. Furthermore it is our belief that heparin rather than Dicumarol is safer and more effective in the early postoperative period.

EARLY DIAGNOSIS AND THE LABORATORY

Up to the present time our chief reliance must still be placed upon a careful history and physical examination in order to suspect the diagnosis and institute prompt treatment. Age does not help one way or the other, as cases from one month to 90 years have been reported. In our group ten of the 12 patients were under 60 years of age. The salient points in the history and physical examination are:

(a) Previous attacks of phlebitis or thrombotic episodes.

(b) A family history of the above.

(c) A prodromal period of vague abdominal discomfort with constipation or diarrhea.

(d) Severe abdominal pain, often colicky, out of all proportion to the physical findings, and difficult to relieve with the usual doses of opiates.

(e) Marked abdominal tenderness with comparatively little spasm.

(f) Only slight temperature rise.

(g) Blood on rectal examination.

Suspicious laboratory findings are:

(a) Leukocytosis of 15,000 to 25,000 with neutrophiles 80 to 90 per cent.

(b) Polycythemia, real or due to dehydration.

(c) Positive guaiac test in stool or vomitus.

(d) Anemia.

(e) High hematocrit.

It would be most helpful were some comparatively simple test available to aid us in the early diagnosis of this obscure manifestation of intravascular

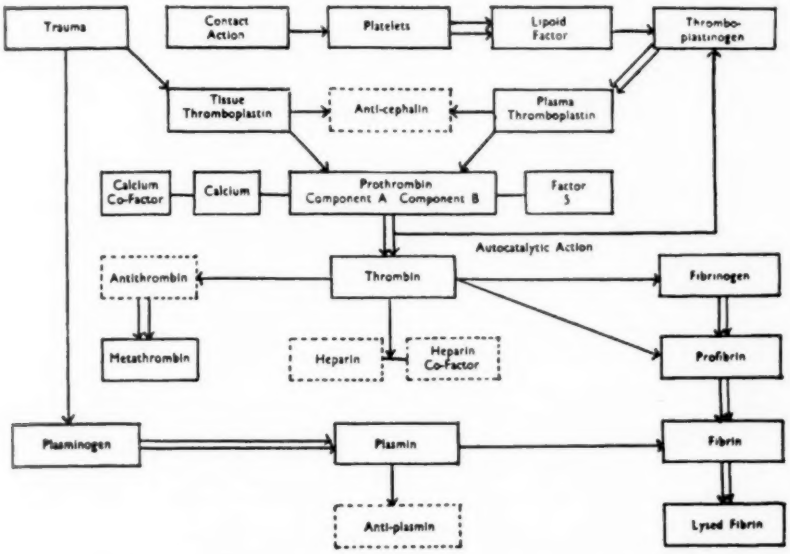

FIG. 1.—A diagrammatic synthesis of the factors probably concerned in coagulation, and their interrelationship. A single arrow signifies "reacts with." A double arrow signifies "produces." A line joining two factors signifies "in conjunction with," more precise information in this case being not available. Anticoagulant factors are outlined with a dotted line. (Macfarlane, R. G.: Normal and Abnormal Blood Coagulation. J. Clin. Path., 1: 113 (May) 1948.)

coagulation. According to Macfarlane,[34] "this mysterious and unpredictable occurrence apparently is not primarily due to an abnormality of the blood-clotting mechanism, but to the combination of tissue damage and circulatory stasis that may displace the clotting-anticlotting equilibrium in favour of coagulation."

Quick,[35] in a recent letter says: "One must not overlook the fact that the coagulation time is entirely empyric and totally unphysiologic. While a prolonged coagulation time denotes an abnormality in the coagulation reaction, a normal value gives no assurance that the coagulation mechanism is normal or that hemostasis is adequate. . . . With a test that is as poorly controlled

as the coagulation time, it is difficult to determine how much shortening must occur before a state of hypercoagulability exists."

A vast amount of work has been done on intravascular clotting over the past quarter century, yet the problem is still complicated and there is tremendous disparity between *in vitro* and *in vivo*. The classical conception of the clotting of blood was stated by Morawitz almost 50 years ago.[34]

1. Prothrombin + Ca + Thromboplastin = Thrombin
2. Fibrinogen + Thrombin = Fibrin

Our present conception, however, is completely different, as may be seen in the diagram reproduced with the kind permission of Dr. R. G. Macfarlane, and the *Journal of Clinical Pathology*, from his article on "Normal and Abnormal Blood Coagulation," in the May, 1948, issue (Figure 1).

TABLE VII.—*Follow-up Studies and Survivors.*

Case	Time	Status	Platelets	Coagulation Tests
1	5 years	Well	Normal	Protamine titration...Normal Clotting time.....8-10 minutes
1A	2 years	Well on Dicumarol	Normal	Prothrombin time....17.8-52.9 seconds (normal 14 ±1)
7	1 year	Well	Normal	Clotting time.....5 minutes Prothrombin time....12.2 seconds (normal 14 ±2)
10	6 months	Well	Normal	Protamine titration...Normal Clotting time.....8 minutes Prothrombin time....20.2 seconds (normal 16 ±2)
11	2 years	Well	Normal	Protamine titration...Normal Clotting time.....10 minutes Prothrombin time....16.1 seconds (normal 08 ±2)

In spite of the pitfalls of inaccuracy, some of the simpler laboratory studies might well be of benefit in establishing a diagnosis and in follow-up studies (Table VII). The most familiar of these are:

1. Coagulation time.
2. Prothrombin level.
3. Platelet count.[34, 36]
4. Clot retraction time.[37, 38]
5. Hematocrit.

Quick[36] believes that his prothrombin consumption determination is of considerably more value than the simple prothrombin time. This, and other determinations such as protamine titration, and the studies on alpha tocopherol phosphate by Ochsner and his group, may prove to be of benefit in the follow-up of these patients.

SUMMARY AND CONCLUSIONS

1. A review of agnogenic venous mesenteric thrombosis has been given.
2. Thirteen examples in 12 patients have been described and their case histories presented.

3. There were five recoveries; one patient survived two attacks.

4. All the successful cases were operated upon, and in four anticoagulants were administered postoperatively.

5. The difficulties of correct diagnosis are recognized; in only two instances in our series was a correct diagnosis made.

6. Suggestions concerning laboratory aids in diagnosis and in follow-up studies have been made.

7. In order to lower the mortality a strong plea has been made for the early recognition of an acute abdominal emergency, early operation, and immediate institution of anticoagulant therapy with heparin postoperatively.

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AWARD FOR OUTSTANDING RESEARCH IN THE FIELD OF INFERTILITY

The American Society for the Study of Sterility offers an annual award of $1000 known as the Ortho Award, for an outstanding contribution to the subject of infertility and sterility. Competition is open to those in clinical practice as well as individuals whose work is restricted to research in the basic sciences. Essays submitted for the 1951 contest must be received not later than March 1, 1951. The Prize Essay will appear on the program of the 1951 meeting of the Society. For full particulars, address The American Society for the Study of Sterility, 20 Magnolia Terrace, Springfield, Mass.

SUDDEN AND COMPLETE OCCLUSION OF THE PORTAL VEIN IN THE *MACACA MULATTA* MONKEY*

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LIMITED AS IT IS by two capillary beds, the portal circulation is unique. Furthermore, it is an invariable characteristic of the venous drainage of the gastro-intestinal tracts of all vertebrates. So striking and unusual has this vascular system appeared that it has been assumed to have some special functional and anatomical significance. For these reasons, teleological as they are, the portal circulation has long interested anatomists, physiologists, and biochemists. More recently, with the discovery that certain defects in the cardiovascular system are amenable to operative correction, surgeons have evidenced increasing interest in the physiology of the portal circulation. Chiefly has attention been paid to lowering portal hypertension by constructing an anastomosis between the portal and systemic venous beds. In addition, interest has been expressed in the possibility of resecting the portal vein if it be found invaded by a malignant tumor.

Our interest in the portal system originated in studying the feasibility of excising the portal vein if invaded by cancer. As the experiments progressed, however, it soon became evident that opportunities were arising to solve some of the problems encountered in normal and abnormal portal physiology and hemodynamics. Shortly we found that our major efforts were being directed toward explaining the etiology of portal hypertension. Although the experiments which we shall report cannot be considered complete we do not apologize for their presentation at this time. Certain aspects have proved so provocative that we feel they must prove of interest to those concerned with this phase of vascular surgery.

It is a common belief among members of the medical profession that sudden and complete occlusion of the portal vein is promptly fatal. Ample evidence can be found that this is the sequence of events in the usual laboratory animals such as the rabbit, cat, and dog. When, however, such information as is available upon this subject in the human being is studied, the evidence clearly indicates that in man the inevitability of death following acute portal obstruction may be doubted.

Credit for the earliest observations on this phenomenon in animals must be given to Oré,[1] to Schiff,[2] and to Claude Bernard.[3] Working in 1856, 1863,

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and 1877 respectively, these men proved that sudden occlusion of the portal vein in rabbits and dogs is promptly followed by death. In explanation of this phenomenon these early experimenters variously offered toxemia, anemia, and liver failure. Within a few years, however, Eck[4] in his classical experiments demonstrated in the dog that death did not follow sudden occlusion of the portal vein if the fistula now bearing his name were constructed between the portal vein and the vena cava. In 1875 Solowieff[5] contributed an additional fact, namely, that the dog could survive total portal occlusion provided its several branches were ligated individually and in stages. The next important observation was that of Neuhof,[6] who in 1913 also demonstrated that this animal survived complete occlusion of the portal vein as long as its lumen was progressively encroached upon at three or four operations spaced a week or so apart. With the exception of a few confusing reports from several continental laboratories, interest in why the cat and the dog die following sudden portal occlusion was not again evinced until 1934 and 1935. At this time Elman and Cole[7] and Boyce[8] reported experiments as a result of which they agreed that loss of effective circulating blood volume was the major cause of death. In addition, Boyce expressed the belief that there was a neurogenic factor involved. In 1945 Brunschwig and Bigelow,[9] patterning their investigations after certain of the earlier experiments, confirmed the fact that the dog tolerated occlusion of the portal vein provided it was performed gradually. In 1947 Schafer and Kozy,[10] in an effort to extend the usefulness of radical pancreatico-duodenectomy, demonstrated in the dog that a portion of the portal vein could be resected if an anastomosis between its distal segment and the inferior vena cava was provided immediately.

From this brief review three conclusions are justified in so far as the common laboratory animals are concerned: first, that they all die more or less promptly following sudden and complete occlusion of the portal vein; second, that the cause of death is shock, primarily due to a sudden diminution of the effective circulating blood volume; and third, that all of these animals survive if provision is made for the escape of blood from the portal to the systemic circulation sufficient in amount to maintain an effective blood volume. This, it has been shown, may be accomplished either directly by an Eck fistula or indirectly by occluding the portal vein in stages. Adequate time must be allowed between operations for the establishment of collaterals.

Upon turning to a consideration of what happens to man following sudden occlusion of the portal vein, it is apparent that any conclusions must be far less definitive. It is quite understandable why surgeons have been reluctant to tamper with the portal vein. In view of the evidence derived from laboratory animals, not only has the portal vein rarely been occluded deliberately, but in addition every effort has customarily been made to avoid damaging this structure. In reviewing this subject in the human being, therefore, it has been necessary to rely for information on such clinical reports as have been published. Accurate evaluation has proved difficult. In nearly all cases in which the portal vein has been ligated the complications of the primary disease or injury have

made any very accurate appraisal of the results of the portal ligation almost impossible. For instance, in 1926 Colp,[11] in an heroic effort to save the lives of patients with suppurative pylephlebitis of appendicular origin, reported three in whom he deliberately ligated the portal vein. Although all three patients lived several days following this procedure, they ultimately died of their primary suppurative disease. Colp did not believe, however, that the cause of death could be assigned directly to ligation of the portal vein. A generous number of comparable experiences could be reviewed, but to no particular end, for Colp,[11] Boyce,[8] and Brunschwig[9] have each published adequate summaries of the reported cases beginning with Gintrac's[12] original article which appeared in 1857. In general, about the only conclusion that is justified at the present time is that man reacts to sudden portal occlusion in a manner quite different from the rabbit, cat, and dog. That he may survive several days or even longer seems obvious, but further than this little can be accepted as proved.

Because it appeared unreasonable to undertake immediately the further study of this problem with man as the experimental animal, and because the experiments reported in the common laboratory animals seemed well substantiated, attention was directed toward one of the primates, the *Macaca mulatta* monkey. This animal was selected for several obvious reasons. In the first place, preliminary investigation revealed that the anatomical relationships of the portal vein, pancreas, and duodenum in this monkey correspond closely to those encountered in the human being. In both, these structures reside in a retroperitoneal position. This, of course, is in direct contrast to the cat and dog, where the pancreas and duodenum occupy an intra-mesenteric position. In the second place, save for one article on hepatectomy (Maddock and Svedberg[13]), no reports could be found indicating that the portal system had been studied in this animal. For convenience in presentation, the various experiments which have been performed to date will be presented and discussed under the following headings:

I. SUDDEN AND COMPLETE OCCLUSION OF THE PORTAL VEIN IN THE MACACA MULATTA MONKEY AND IN TWO PATIENTS WITH INOPERABLE CANCER

Our entire experience with 25 animals in which the portal vein has been suddenly and completely occluded is recorded in detail in Table I. Early in the course of these experiments the portal vein was doubly ligated with silk, while later it was also divided. It is not believed that this difference in experimental technic has materially affected our conclusions. Except where otherwise noted, all of the experiments were performed under open-drop ether. Nineteen of the animals operated upon survived uneventfully, while six died. These six deaths deserve special comment. Three (monkeys No. 28, No. 29, and No. 43) occurred in animals anesthetized with sodium pentobarbital.* Although these deaths may have been due to an advertent overdose

* Veterinary Nembutal Sodium (Pentobarbital Sodium, Abbott), made by Abbott Laboratories; average dose: 0.15 cc. per pound of body weight.

of the drug, it is conceivable that monkeys in which the portal vein has been occluded are less well able to tolerate this barbiturate. This is in accord with Schafer and Kozy's[10] experience with portocaval shunts in the dog. These authors reported abandoning this drug as an anesthetic agent because of a high mortality apparently associated with its use where the portal vein was occluded. Two monkeys (No. 6 and No. 30) received large doses of contrast media in the course of portal venography (vide infra). One was given 30 ml. of Thorotrast while in the other 50 ml. of 70 per cent Diodrast were injected. These, of course, are enormous doses compared upon a basis of body weight with those commonly employed in man. It seems reasonable to believe that the deaths of these two animals should be ascribed to an overdose of these agents rather than to the portal occlusion. One animal (No. 16)

TABLE I.—*Macaca Mulatta Monkey. Summary of 25 Experiments in Which the Portal Vein Has Been Suddenly and Completely Occluded at the Porta Hepatis. Nineteen Animals Survived and Six Died. The Causes of Death Are Discussed in the Text.*

Monkey No.	Vein Occluded		Results
1, 2, 3	Portal	Survived	1 year. Portal circulation reestab.
5	Portal and sup. mes.	Survived	8 mos. Portal circulation reestab.
9, 11	Portal, splenic, and sup. mes.	Survived	1 year. Portal circulation reestab.
17	Portal	Survived	2.5 mos. Portal circ. partially reestab.
18, 19, 21	Portal (Div.)	Survived	7 mos. Portal circulation reestab.
24, 25, 26	Portal (Div.)	Survived	Radical pancreaticoduodenectomy performed
27, 31, 35	Portal (Div.)	Survived	one week after occlusion
37,40, 41	Portal (Div.)	Survived	See Table III
6	Portal and sup. mes.	Died	8 hrs. p. o.? Overdose of Thorotrast
16	Portal	Died	2 days p. o. Dehiscence of abd. wound
28, 29, 43	Portal (Div.)	Died	4 hrs. p. o.? Overdose of sodium pentobarbital
30	Portal (Div.)	Died	1 hr. p. o.? Overdose 70% Diodrast
	Total experiments = 25 { 19 survived, 6 died		

died two days after operation of dehiscence of his abdominal wound and evisceration.

Emboldened by the results obtained in these experiments, we have ligated the portal vein in two patients with inoperable cancer. No untoward sequelae attributable to the portal ligation were detected.

Case 1.—(NYH No. 539941), F.W., age 63. At exploratory celiotomy, this man was found to have a small carcinoma of the lesser curvature of the stomach which had directly invaded the left lobe of the liver. Although the right lobe contained a few small metastatic deposits, it was in no sense replaced by tumor. The portal vein was occluded digitally for an hour and the patient observed for evidence of change in his vital signs. Since none appeared during this period, the portal vein was doubly ligated at the porta hepatis. The patient's recovery from anesthesia was unremarkable and he was discharged from the hospital 23 days after operation. No untoward sequalae attributable to ligation of his portal vein were observed. He died at home two and a half months after his operation. Although autopsy was not obtained, it seemed evident to those observing his terminal illness that death was due to carcinomatosis.

Case 2.—(NYH No. 368488), A.L., age 50. At abdominal exploration this woman was found to have a small cancer in the midportion of the stomach associated with innumerable minute metastatic implants on both peritoneal surfaces. Her portal vein was ligated at the porta hepatis and as in Case 1 no sequelae attributable to her portal occlusion appeared. She died 8 months after operation. Autopsy was obtained, but there was such massive replacement of the upper abdominal viscera with tumor that little could be learned of the effects of her portal ligation. Table II records such postoperative liver function tests as were obtained in these two patients.

No general conclusions concerning portal ligation in man are justified from this meager experience. The most that can be said is that these two patients survived deliberate occlusion of their portal vein without any immediate untoward sequelae which could be detected clinically. Any detailed evaluation of the late effects was quite impossible, for this period was clouded by the progression of their primary gastric cancers. We are well aware, of course, that a measure of criticism may be directed toward these two human experiments. The presence of metastases in the liver may have provided just that amount of intrahepatic block necessary to encourage the formation of sufficient collaterals to permit the survival of these patients. From the appearance of the liver and the veins in the portal bed, however, this possibility is considered unlikely.

II. CIRCULATORY DYNAMICS FOLLOWING PORTAL OCCLUSION IN THE MACACA MULATTA MONKEY

(A) *Effect Upon Systemic Blood Pressure as Measured in the Femoral Artery.* Under open drop ether anesthesia the changes in systemic blood pressure following occlusion of the portal vein were studied. The portal vein was ligated through an upper midline incision and all arterial pressures were taken from the right femoral artery by means of a recording mercury manometer. The results of six such experiments are outlined in Fig. 17. In each instance there was an immediate fall in systemic arterial pressure of about 20 to 30 mm. Hg. Within one to four hours after ligation of the portal vein the arterial pressure had risen to pre-occlusive levels. The results obtained in this type of experiment in the monkey differ dramatically from those reported in the dog. For instance, Elman and Cole[7] proved that in the dog the systemic arterial pressure promptly falls to "shock" levels after occlusion of the portal vein. Here it remains, to be followed within 45 to 70 minutes by death. It is concluded from our experiments that the *Macaca mulatta* monkey can, within one to four hours, return through collateral channels sufficient blood to elevate promptly to normal the slight fall in blood pressure occasioned by sudden portal occlusion.

(B) *The Effect of Sudden Occlusion of the Portal Vein Upon Portal Venous Pressure.* In 15 monkeys measurements of portal venous pressure have been taken before, ten minutes after, and about one week after sudden

TABLE II—(a and b). *Postoperative Liver Function Studies in Two Patients With Inoperable Gastric Cancer in Whom the Portal Vein Was Deliberately Ligated. From a study of These Figures It Can Be Seen That in General, Ligation of the Portal Vein Was Not Followed by Any Changes in the Blood Chemical Values Which Were Obtained.*

(a) Postoperative Blood Chemical Studies and Liver Function Tests Following Sudden Occlusion of the Portal Vein
(Case 1: NYH No. 539941—F.W.—Age 63)

	Hgb.	RBC	WBC	Prothrombin			Urea	Sugar	Protein			Phos.	Ict. Ind.	S. Bilir.	T. Chol. Chol. E.	BSP	Alk. Phos.	T.T.	C.F.
				Undil.	Dil.	St'd.			Total	Alb.	Glob.								
Pre-op.	14.9	4.9	11.0	17.0	32.4	42.7	21	...	7.9	...	...	...	...	0.4	...	...	...	...	...
Ligation portal vein	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
P. O. 1	13.0	...	...	...	...	...	...	...	...	...	...	...	...	...	194	...	...	...	...
P. O. 2	13.0	...	...	17.7	35.7	43.1	...	92	...	...	...	3.6	...	0.1	...	...	13.1	9	...
P. O. 3	12.8	4.2	14.3	13.9	31.2	42.0	...	95	...	...	...	2.3	...	1.0	198	...	10.3	9	9
P. O. 5	...	...	...	15.3	33.9	44.2	...	...	...	...	...	2.6	...	0.2	194	...	12.8	8	11
P. O. 6	...	...	...	15.2	35.2	42.1	...	83	...	...	...	...	...	...	...	...	...	...	...
P. O. 8	...	...	...	17.1	37.5	42.0	...	71	...	...	...	2.9	...	0.7	181	...	14.9	7	13
P. O. 9	...	...	...	18.6	37.3	42.5	...	...	...	...	...	2.4	...	0.5	152	...	15.1	7	...
P. O. 10	...	...	...	16.3	41.5	43.2	...	84	...	...	...	...	...	...	...	...	...	...	...
P. O. 12	...	...	...	...	...	...	...	80	...	...	...	2.9	...	0.5	189	...	19.3	8	11
P. O. 14	...	...	...	...	...	...	...	71	...	...	...	2.5	...	0.5	157	...	15.4	8	12
P. O. 21	...	...	...	...	...	...	...	75	...	...	...	3.2	...	0.5	174	...	23.1	...	14
												3.2	...	0.1	204	...	22.5	10	15

(b) Postoperative Blood Chemical Studies and Liver Function Tests Following Sudden Occlusion of the Portal Vein
(Case 2: NHY No. 368488—A.L.—Age 59)

	Hgb.	RBC	WBC	Prothrombin			Urea	Sugar	Protein			Phos.	Ict. Ind.	S. Bilir.	T. Chol. Chol. E.	BSP	Alk. Phos.	T.T.	C.F.
				Undil.	Dil.	St'd.			Total	Alb.	Glob.								
Pre-op.	12.6	3.8	6.9	15.2	32.6	40.4	14	...	6.9	5.4	1.5	...	...	...	...	...	...	...	...
Ligation portal vein	...	...	...	...	...	...	13	218*	...	...	...	...	...	...	...	...	...	...	...
P. O. 1	11.1	3.5	...	...	...	...	12	89	6.6	5.0	1.6	3.4	5	...	...	3.4	3.1	1	...
P. O. 2	13.3	3.1	...	14.4	32.9	37.0	9	103	6.7	4.9	1.8	3.5	4	...	...	...	2.4	1	6
P. O. 3	...	...	...	...	...	...	11	101	6.5	4.9	1.6	3.9	4	...	258/195.5	...	2.6	0	6
P. O. 6	...	...	...	...	...	...	...	97	...	...	...	...	...	0.8	...	...	...	1	...
P. O. 10	...	...	...	13.8	35.6	37.5	10	...	5.9	4.2	1.7	...	...	...	...	2.8	3.1	...	6
P. O. 20	11.5	3.9	5.3	...	...	...	...	...	7.9	5.3	1.7	...	...	...	...	1.4	...	2	...
P. O. 150	10.9	3.5	4.9	...	...	...	13	82	6.3	4.5	1.8	...	...	0.3	...	0	...	...	...

* Probably due to a glucose infusion administered during operation.

occlusion of the portal vein.* After determining the normal level of pressure within the portal venous system, the portal vein has been divided between two ligatures of silk. It was found that it required approximately ten minutes for the pressure to reach a stable level. Upon ascertaining the degree of hypertension immediately produced by portal occlusion, the abdominal wounds were closed and the animals permitted to recover. One week after division of the portal vein the abdomens of these monkeys were again opened and the portal pressure measured in a vein as near the one employed initially as possible. In a few animals portal pressures were obtained daily after occlusion and it was interesting to note that a fall toward normal began within 24 hours. Because a daily celiotomy was found to be more than these animals could tolerate equably, most of the late measurements have been taken at the end of about one week.

Figure 18 summarizes the results of some 40 measurements taken on 15 monkeys. Normal values were found to fluctuate from 9 to 18 cm. of saline. No specific explanation could be found to account for this rather wide variation. Ten minutes after portal occlusion the values varied from 24 to 57 cm. of saline. The pressure levels observed at the end of one week were curiously constant. Although there was a marked fall recorded in each animal, there was no instance of complete return to pre-occlusive levels. There always was evident at this time a minor degree of portal hypertension, usually, however, amounting to no more than a centimeter or two of normal saline. No levels of portal hypertension comparable to those seen in human beings suffering from this disease have been obtained. Experiments are currently being performed in an effort to explain this discrepancy.

(C) *Portal Venography Following Sudden and Complete Occlusion of the Portal Vein.* Early in the course of these experiments, efforts were made to follow the changes in portal hemodynamics at autopsy or at an exploratory celiotomy. Postmortem observations were particularly disappointing, for the small collateral veins collapsed and little significant information was obtained. Examination of the vessels in the portal bed at exploratory celiotomy proved only slightly more informative, for its extent was of necessity limited. In a few instances where exploration was performed, two, three, and nine months after portal vein occlusion, there presented a remarkable picture of dilatation

* All of these values have been obtained by inserting a 20-gauge hollow needle into a major vein of the jejunal mesentery approximately 5 cm. beyond the ligament of Treitz. Pressures have been measured by means of a spinal manometer filled with normal saline. The details of this technic are illustrated in Figure 1. The pressure is determined by filling the manometer well above the anticipated level and then permitting the saline to run into the mesenteric vessel. The pressure existing in the portal venous system is accepted to be at that level at which the saline in the manometer and the blood in the mesenteric vein reach equilibrium. In every instance the final value has not been recorded until a fluctuation of a few millimeters was noted in the level of the saline in the manometer. This fluctuation, coincident with respiration, is believed to be an indication that the system is unobstructed and that the readings obtained accurately reflect portal venous pressure.

FIG. 1

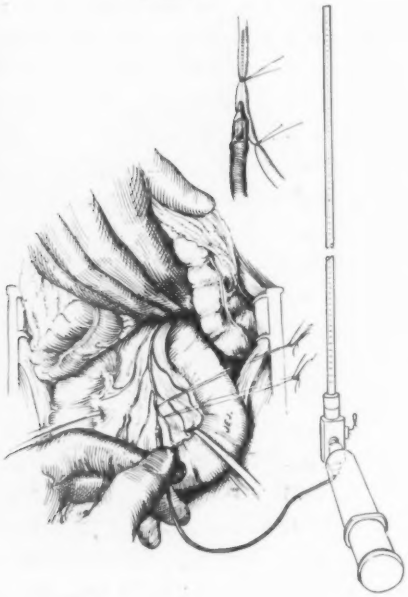
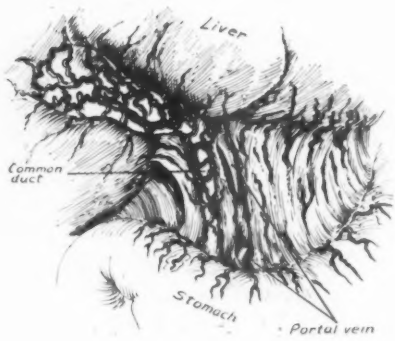
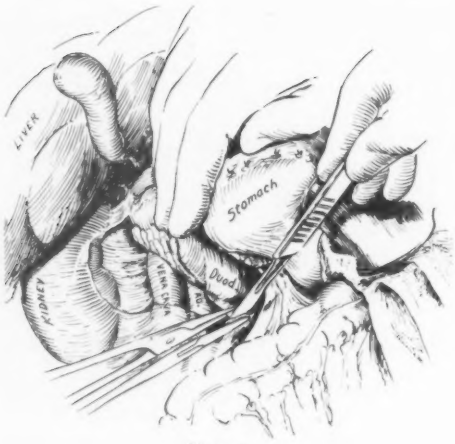


FIG. 2





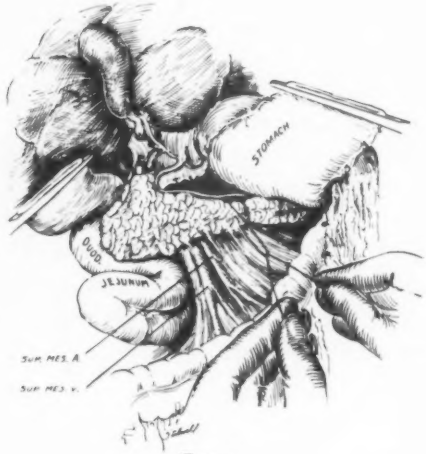


FIG. 3

FIG. 4

FIG. 1.—Technic of measuring portal venous pressure in centimeters of saline with a standard spinal manometer.

FIG. 2.—*Macaca Mulatta* Monkey. Artist's conception of the marked venous dilatation developing over the surfaces of the gall bladder and common duct and within the gastrohepatic ligament at about four months after ligation and division of the portal vein. This picture corresponds closely to that described in humans with an extrahepatic portal block.

FIG. 3.—*Macaca Mulatta* Monkey. First step in resection of the pancreas, duodenum, and portal vein. This involves separating the distal third of the stomach from the hepatic flexure of the colon. In addition the lateral peritoneal reflection of the duodenum is completely divided.

FIG. 4.—*Macaca Mulatta* Monkey. Following mobilization of the duodenum and head of the pancreas, the common duct and pancreaticoduodenal artery are divided. The splenic and superior mesenteric arteries are, of course, carefully preserved. At this point the pancreas and splenic veins are divided between ligatures to permit reflection of the entire specimen to the right side of the animal and to expose the portal and superior mesenteric vein.

of the veins in the gastrohepatic ligament and of those on the surface of the common duct and gall bladder. An artist's conception of the hemangiomatous conversion of the superficial veins of the normal structures found in the right upper quadrant is reproduced in Figure 2. Although this is indeed an intriguing picture in that it corresponds closely to that occasionally encountered in portal block in man, neither of these two methods of study proved satisfyingly informative. Recourse was then taken to portal venography as reflected in a roentgen-ray film taken during the course of injecting 35

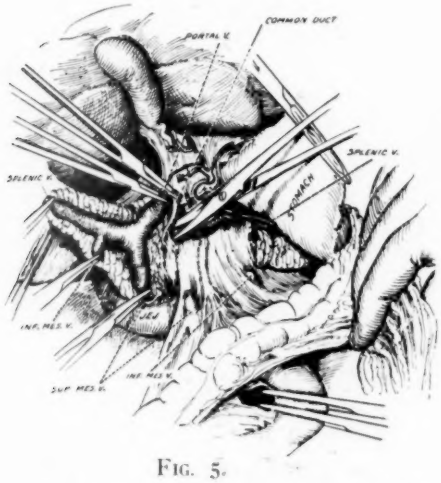


FIG. 5.

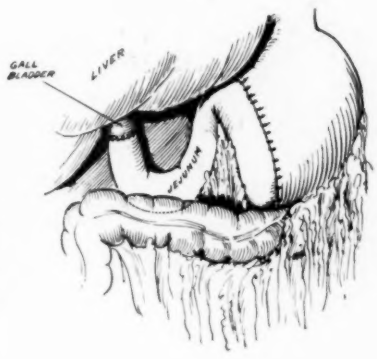


FIG. 6

FIG. 5.—*Macaca Mulatta Monkey.* The entire specimen (head of the pancreas, common duct, duodenum, and the junction of the portal, splenic, and superior mesenteric veins) is reflected to the right side of the animal and its removal completed. The upper few centimeters of jejunum are included in the resection to insure the viability of bowel with which the enteric canal must be reconstructed.

FIG. 6.—*Macaca Mulatta* Monkey. Reconstruction of the enteric canal by means of an end-to-end cholecystojejunostomy and an end-to-side gastrojejunostomy. Both anastomoses are performed in the retrocolic position. Pancreaticojejunostomy is omitted in order to facilitate the procedure.

per cent of 70 per cent Diodrast directly into the portal system. All of the injections were made into a vein in the jejunal mesentery through a small midline incision with the animals under light ether anesthesia. Figures 9 to 11 are representative portal venograms obtained immediately, one, four, and 12 months after sudden and complete occlusion of the portal vein. In Figure 8 is reproduced a normal portal venogram.

The information obtained from examination of 22 portal venograms demonstrates clearly that immediately after ligation portal blood gains access to the systemic circulation primarily through pelvic anastomotic channels, through the hepatopetal vessels, and probably through the other hepatofugal channels conventionally described as being called into play in the human being when the portal vein is blocked. At the end of about two months it is

obvious that the site of occlusion or division of the portal vein is beginning to be by-passed and blood is gaining access to the liver directly. Progressively, the hepatopetal plexus of veins expands so that by the end of a year, and probably earlier, the portal blood traverses the liver normally. With the hepatopetal circulation widely opened the hepatofugal system closes and literally cannot be filled in the course of portal venography. Some criticism can be justly leveled at this method, for no effort has been made to inject the contrast medium at pressures only slightly above those existing in the portal circulation. For instance, in Figure 9 the splenic pedicle is clearly outlined. This is positive evidence that the pressure of injection was higher than it should have been, for we have proved in six experiments that if the splenic vein is ligated following portal occlusion, there is a drop in the portal pressure averaging about 10 cm. of saline. Thus, as in the human being, the splenic venous drainage contributes about 10 per cent to the total value of portal hypertension. Another example indicating that the pressures employed in injecting the portal system have been excessive is found in Figure 13. This portal venogram, obtained after occlusion of the portal vein in monkey No. 30, reflects an injection of 50 ml. of 70 per cent Diodrast within a few seconds. Here are demonstrated innumerable channels which cannot usually be identified, and which undoubtedly indicate injection at an excessively high pressure.

FIG. 7.—Picture of monkey No. 35 five days after resection of the pancreas, the duodenum, and the portal vein.

With some trepidation, portal venography was performed in two human beings (Cases 1 and 2—vide supra) immediately after portal occlusion. These venograms are reproduced in Figures 14 and 15. The close similarity between the films obtained in man and monkey is of interest, and presents further evidence that the portal circulation in these two species is nearly identical. It is understandable that these studies in man could not be repeated at intervals following the occlusion.

III. MICROSCOPIC STUDIES ON BIOPSIES OF THE LIVER OBTAINED SERIALLY AFTER PORTAL OCCLUSION

From 15 monkeys, biopsies of the liver were obtained by exploratory celiotomy at intervals of from one week to one year following portal occlusion.

FIG. 8

FIG. 9

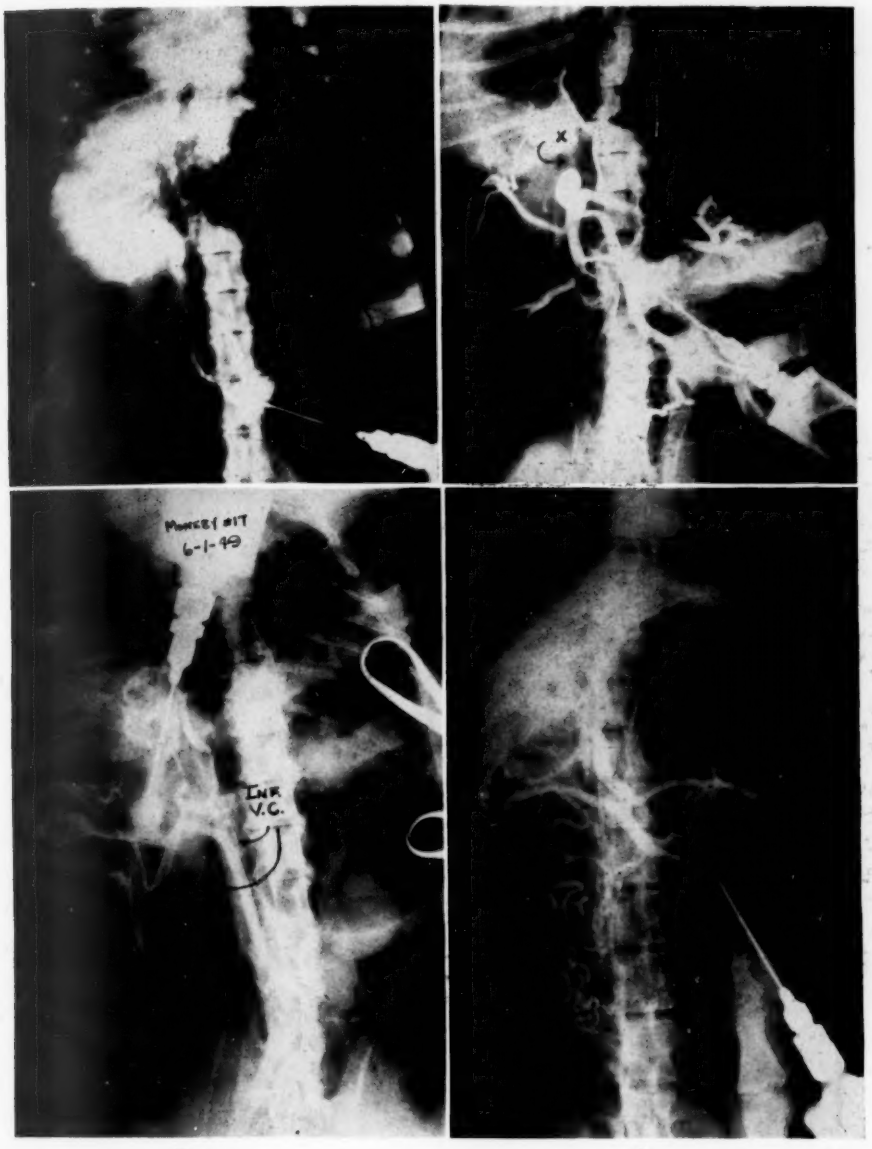


FIG. 10

FIG. 11

FIG. 8.—*Macaca Mulatta* Monkey. Normal portal venogram.

FIG. 9.—*Macaca Mulatta* Monkey. Portal venogram obtained immediately after complete and sudden occlusion of the portal vein. The fact that the splenic pedicle is outlined probably indicates that the contrast medium was injected at an excessively high pressure.

FIG. 10.—*Macaca Mulatta* Monkey. Portal venogram obtained one month after portal occlusion. The majority of the radiopaque dye disappears into the pelvis, returning, however, promptly and in sufficient concentration to outline the inferior vena cava and both iliacs. Already a small amount of dye is gaining access to the liver directly through the hepatopetal system of veins lying in the gastrohepatic ligament.

FIG. 11.—*Macaca Mulatta* Monkey. Portal venogram obtained four months after occlusion.. Here direct filling of the liver is almost complete.

FIG. 12 FIG. 13

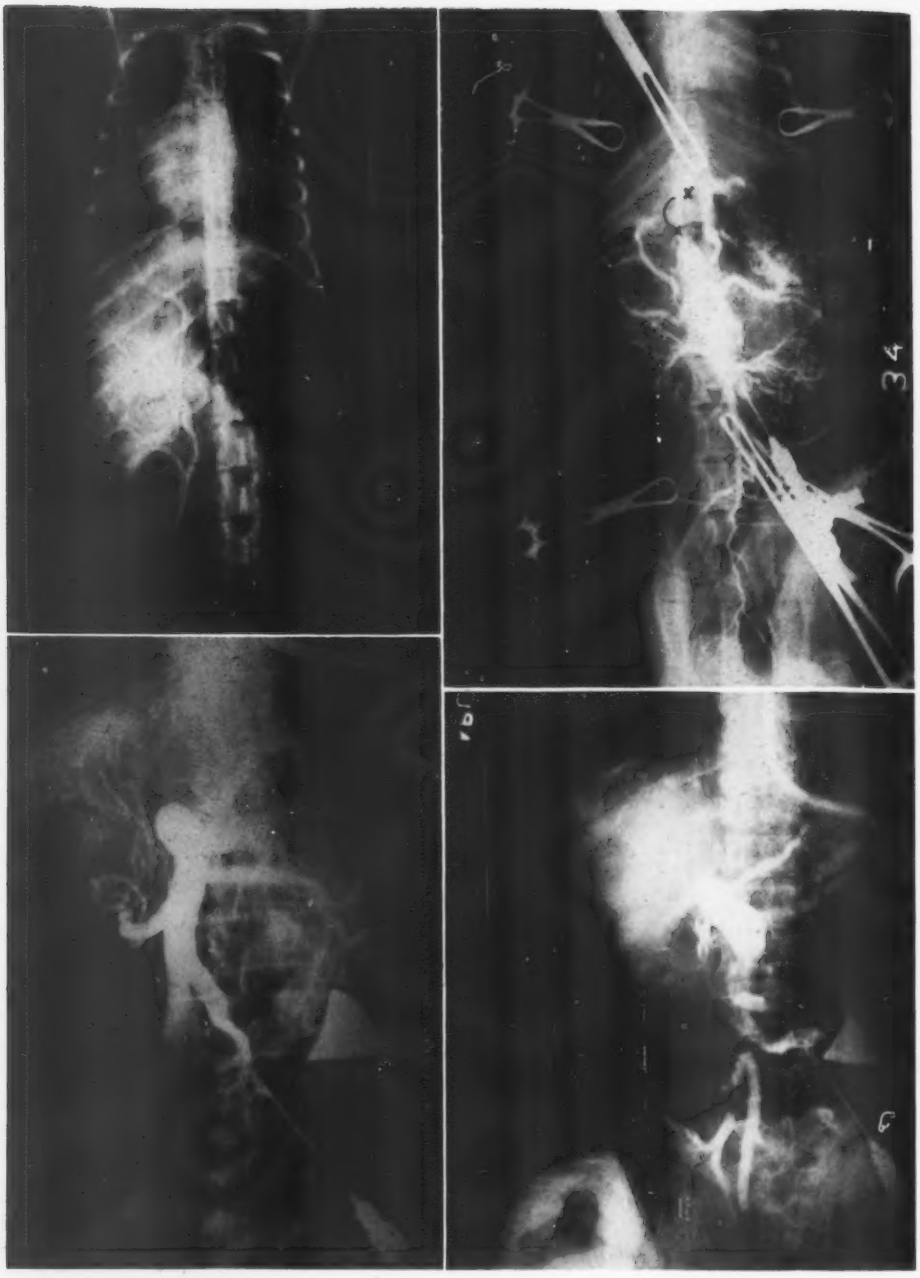


FIG. 14 FIG. 15

FIG. 12.—*Macaca Mulatta* Monkey. Portal venogram at one year. The site of occlusion is now completely by-passed and filling of the liver is direct.

FIG. 13.—*Macaca Mulatta* Monkey. Portal venogram obtained immediately after occlusion of the portal vein. X = point of occlusion. This film was obtained with 50 ml. of 70 per cent Diodrast injected under what is assumed to be excessive pressure. Note extensive filling of even minute radicals.

FIG. 14.—NYH Case 1. Portal venogram obtained immediately after deliberate occlusion of the portal vein.

FIG. 15.—NYH Case 2. Portal venogram obtained immediately after deliberate occlusion of the portal vein.

A total of 24 hepatic biopsies were examined and in no instance could any evidence of morphologic change be identified.

IV. MISCELLANEOUS OBSERVATIONS

As the occasion arose, the livers and spleens of these animals were observed grossly for evidence of change in their appearance. Immediately after ligation of the portal vein the liver apparently shrinks in size ever so slightly while the spleen appears to become engorged. At subsequent abdominal operations, similar observations were made wherever possible, and no gross abnormalities noticed. In no instance has one of these animals developed gross enlargement

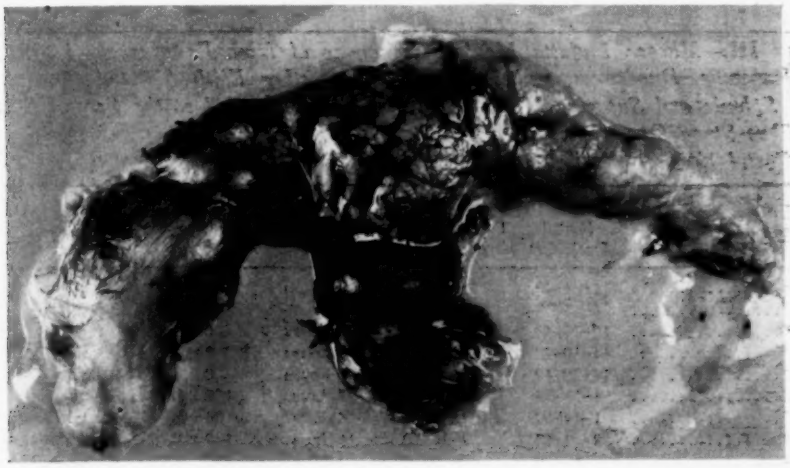


FIG. 16.—*Macaca Mulatta* Monkey. Photograph of specimen removed from monkey No. 40 demonstrating the extent of the portal resection.

of the spleen. Of passing interest is the fact that ascites has never developed. This, of course, is in accord with the recently reported observations of Volwiler, Grindlay, and Bollman[14] and of McKee, Schloerb, Schilling, Tishkoff, and Whipple.[15] These authors report that in the normal dog, ascites does not form unless the hepatic veins are constricted. In a number of our animals, dilated veins have appeared on the anterior abdominal wall about two weeks after ligation of the portal vein. These, persisting for a few weeks and then disappearing, probably reflect a very transient period of minimal portal hypertension.

V. PANCREATICODUODENECTOMY WITH PARTIAL RESECTION OF THE PORTAL, SPLENIC, AND SUPERIOR MESENTERIC VEINS

Having proved that the *Macaca mulatta* monkey could tolerate sudden and complete occlusion of the portal vein, we next attempted to resect the pancreas, duodenum, and portal splenic, and superior mesenteric veins. These

operations followed closely the pattern described for man by Child[16] in 1948 with the exception that no effort was made to perform a pancreaticojejunostomy. This was omitted because it did not seem essential to the experiment. Of seven monkeys in which a one-stage operation has been performed, six died on the table from shock due to blood loss, while for some unexplained reason one animal survived for 24 hours. As soon as the portal and superior mesenteric veins were ligated in these animals bleeding became quite uncontrollable. Although hemostasis had been painstaking, the entire operative field oozed copiously as soon as the portal vein was occluded. Uncontrollable venous bleeding was particularly striking as soon as an effort was made to perform the gastro- and cholecystojejunostomy necessary for

TABLE III.—*Macaca Mulatta Monkey. Summary of Nine Experiments in Which the Pancreas, Duodenum, and Portal Vein, Together With Short Segments of the Splenic and Superior Mesenteric Veins, were Resected at the Second Stage of a Two-Stage Operation. The First Stage Consisted in Ligation and Division of the Portal Vein at the Porta Hepatis.*

Monkey No.	Portal Occlusion	Radical Pancreaticoduodenectomy	Survival Time	Blood Transfusion	Cause of Death
24	11-28-49	12- 6-49	5 hours	0	Shock
25	11- 3-49	11- 9-49	2 days	0	Acute gastric dilatation
26	10-31-49	11- 2-49	5 hours	0	Shock
27	11-10-49	11-16-49	5 hours	0	Shock
31	11-29-49	12- 7-49	6 hours	0	Shock
35	1-16-50	1-24-50	7 days	100 ml.	Peritonitis
37	1-19-50	1-31-50	4 days	80 ml.	Gastric dilatation
40	2- 9-50	2-24-50	16 days	100 ml.	Infection abd. wound
41	2-10-50	2-20-50	4 hours	100 ml.	Shock

reconstruction of the enteric canal. From these seven experiments it was concluded that any operation in the monkey deliberately contemplating pancreaticoduodenectomy and resection of the portal vein in one stage was unsound. Arguing by analogy, any such one-stage operation should not be attempted in man.

Having discovered, as outlined above, that within a week after portal occlusion the portal pressure fell nearly to normal, we turned our attention to a two-stage procedure. At the first stage the portal vein has simply been ligated and divided; at the second stage, performed from five to ten days later, it has been found possible to resect the pancreas and duodenum together with the portal vein. The uncontrollable hemorrhage reported in the one-stage operation was not encountered. Table III outlines our experience with nine two-stage resections. Although five of the nine animals were in severe shock at the end of the operation, they all survived five to six hours. In the remaining four animals the survival time was prolonged from this short period to from two to 16 days by giving these animals 80 or 100 ml. of citrated blood at the close of the procedure. It has been a disappointment, of

course, that we have been unable to secure longer periods of survival, but when the causes of death are studied it seems obvious that our animals have died because of our inability to give them even a small degree of modern postoperative care. All of the postoperative complications so dreaded a decade or two ago have appeared and have, we believe, accounted for these failures. Peritonitis, hypoproteinemia, wound sepsis, and acute gastric dilatation have all been observed. At the present time we are engaged in attempting to persuade our animals to accept chemotherapy, parenteral fluids (including blood transfusion), and gastric aspiration. If this is permitted, we believe we may anticipate a reasonable degree of success in keeping our monkeys alive following this radical surgical procedure. In spite of this high mortality rate it has been demonstrated that if the operation is performed in two

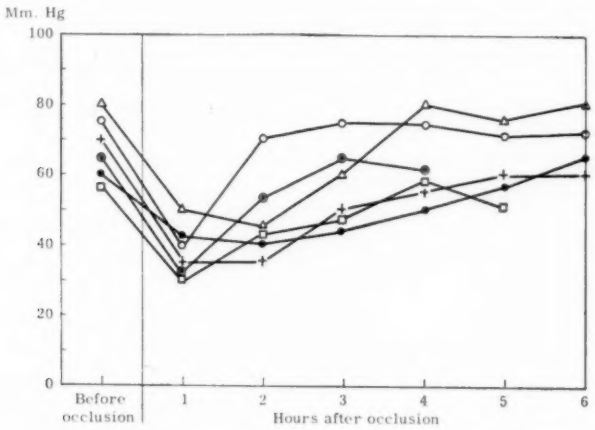


FIG. 17.—*Macaca Mulatta* Monkey. Composite graph of the changes in systemic blood pressure appearing in six monkeys after sudden and complete occlusion of the portal vein. Following a prompt fall of 20 to 30 mm. Hg., the systemic blood pressure rose to normal within one to four hours in all of these animals.

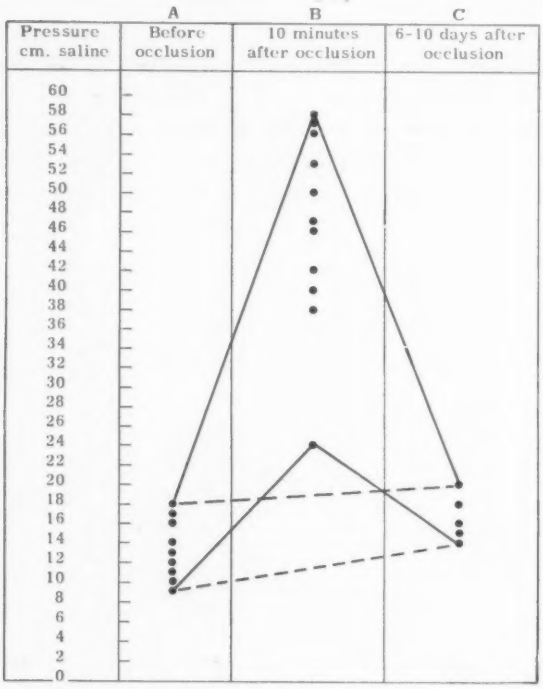
stages the monkey can survive the readjustments in the circulatory dynamics necessary for successful resection of his pancreas, duodenum, and major portal veins. Figures 3, 4, 5, and 6 outline in some detail the type of operation performed at the second stage in these experiments. Figure 16 is a photograph of one of the specimens removed and Figure 7 is a picture of monkey No. 40 five days after operation.

Numerous obvious objections must, of course, be raised if this two-stage operation is proposed for the treatment of patients with pancreaticoduodenal cancers which have invaded the portal, splenic, or superior mesenteric vein. In the first place, it has not been proved that all human beings can tolerate sudden and complete occlusion of the portal vein. In the second place, it can be postulated that if these structures are invaded, the tumor has already progressed beyond the realm of possible cure. And to be sure, the late

results of deliberate portal occlusion in man have not yet been satisfactorily determined.

SUMMARY AND CONCLUSIONS

The purpose of these experiments has been, of course, to attempt to clarify certain unsolved problems in portal physiology. We believe that we have proved that one animal at least, the *Macaca mulatta* monkey, can tolerate sudden division of its portal vein. Aside from its specific interest, this fact is of further significance, for it has served to demonstrate one of the



Monkey No.	A Before occl.	B 10 min. after occl.	C 6-10 days after occl.
24	16	24	17
25	14	57	20
26	13	38	18
27	13	53	18
28	9	56	
29	9	50	
30	18	47	
32	12	40	15
31	9	58	16
33	9	50	
34	17	42	
35	10	57	17
37	11	46	12
40	13	50	14
41	9		14

FIG. 18.—*Macaca Mulatta* Monkey. Changes in portal venous pressure occurring ten minutes and one week after occlusion of the portal vein. Immediately there is a rise of from 20 to 50 cm. of saline. Within a week this has fallen almost to normal.

pitfalls of surgical research, namely, that of applying uncritically to man facts proved true in laboratory animals. Undoubtedly a portion of our belief that man does not tolerate sudden portal occlusion well is derived from the demonstrated fact that the dog succumbs promptly after such a procedure.

One man and one woman have survived deliberate occlusion of the portal vein without detectable untoward sequelae which could be attributed to interruption of the portal blood flow. Before any generalizations are possible for man, however, many more such experiments will have to be performed. Because this opportunity arises but seldom in any one hospital, this is considered a fertile field for general investigation in hospitals throughout the country.

It has been a great temptation to conjecture why our animals have not maintained a degree of portal hypertension comparable to that encountered

in human beings with extrahepatic portal block. Perhaps the monkey is able to open collaterals more widely and more quickly than can man. Perhaps portal hypertension is, as some believe, a manifestation of disease primary in the portal vein and its tributaries. These as well as other possible explanations have proved attractive, but the fact of the matter is that before any conclusions in this regard can be drawn much more work will have to be done. At the present time this too will have to stand as an observation without adequate explanation.

In addition, we believe that we have proved that the monkey can tolerate for a time (at least several days) the circulatory readjustments necessary to permit resection of the portal vein enbloc with the lower stomach, the duodenum, and the pancreas. Whether uneventful survival periods of months or even years can be obtained following such experiments remains to be proved. And it must be proved that these animals can be maintained in good health for long periods of time before any thought is given to the application of the operation to man for the cure of pancreaticoduodenal cancers.

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DISCUSSION.—DR. ALTON OCHSNER: The question of venous thrombosis has become increasingly more significant, because it is a more prevalent condition than previously.

As you know, in New Orleans we have been interested in venous thrombosis for a number of years, and for a number of years felt that we could do something to prevent the occurrence of this complication.

We have gone over a series of 1002 cases at the Charity Hospital in the last 11 years—1002 cases of phlebothrombosis, thrombophlebitis and/or pulmonary embolism, and I would like to give you some of the results of that study.

[Slide] It is not only the number of cases but the progressive increase in the number of cases which seems to us extremely important. In spite of the measures that we

have undertaken to prevent this, there has been a progressive increase over the years, particularly in the cases of thrombosis, somewhat more than the fatal cases.

[Slide] In breaking this down into the different series, and comparing with the total fatalities, you will see in the medical and surgical series the incidence of fatal pulmonary embolism is about comparable to the total fatalities. There are two discrepancies. One is on the tuberculosis service and the other is on the gynecologic service. The reason for the high incidence of fatal pulmonary embolism on the gynecologic service is undoubtedly due to the fact that in New Orleans we have a large number of criminal abortions done by midwives which are admitted to the gynecologic service. I cannot explain the low incidence on the tuberculosis service.

[Slide] Venous thrombosis is potentially a fatal disease. Forty-one per cent of all the patients who had thrombo-embolism in the Charity Hospital died. The fatality incidence is highest on the medical service, because of the high incidence of coronary disease, and it is lowest on the obstetric service, because these patients have true thrombophlebitis, which seldom kills.

[Slide] We attempted to determine whether it would be possible—from the examination of these patients or their records—to determine whether they had an antecedent thrombosis, and, as you can see here, in over 40 per cent of the instances of fatal pulmonary embolism, there was no clinical evidence of an antecedent thrombosis showing the significance of this condition.

[Slide] We have been interested in another phase of venous thrombosis, namely, the antithrombin content of the plasma. Dr. Kay, working in our department for the past two years, has shown that there is apparently a relationship between the incidence of venous thrombosis and the antithrombin content. If one does antithrombin determinations preoperatively and in the successive days postoperatively, one will see that normally there is a decrease in antithrombin, which, after a period of four to five days, attains its normal level. However, in the individuals who develop thromboses, there is a progressive fall in antithrombin.

[Slide] We feel that the antithrombin content is the important factor in the production of these thromboses. We have had 238 patients who have been subjected to major surgical procedures, of whom 145 have had antithrombin levels of 1 to 16 or higher. There was one non-fatal pulmonary embolus in this group, on the fifth postoperative day, with an antithrombin level of 1 to 16, and a prothrombin time of 15 seconds.

[Slide] There were 93 antithrombin levels of less than 1:16. Nineteen developed intravascular clotting. Four had fatal pulmonary emboli and one died of cerebral thrombosis.

In these patients who have had low levels, we have been using alpha-tocopheral as a normal antithrombin. If one will give alpha-tocopheral to these individuals, combined with calcium—either as the phosphate or the acetate, depending upon whether they can take it by mouth—the antithrombin level can be kept high.

We have had 175 cases in which this has been used. There was one that had a level below 1 to 16 on the first postoperative day before treatment. One patient had a non-fatal embolus on the second day postoperatively, and died with a pulmonary embolism on the tenth postoperative day. This patient had a pneumonectomy. We believe she had her clot before she was operated on, because on her second postoperative day, at the time of withdrawal of her oxygen, she had dyspnea and cyanosis. We interpreted that as due to withdrawal of oxygen, but I am sure this was incorrect.

The determination of antithrombin—or a high or normal antithrombin—does not mean the patient does not have a thrombus already present. However, we do believe it is not possible for a patient to develop a thrombus as long as the antithrombin is kept high. The advantage of antithrombin determination, and the administration of alpha-tocopheral, in our minds, is that it prevents the thrombosing tendency without

producing a hemorrhagic tendency. We have not hesitated to give alpha-tocopheral and calcium to patients who have had transurethral prostatic resections and other operative procedures which are likely to be associated with postoperative bleeding.

DR. CARLOS A. TANTURI: Previous in-vitro studies done in the surgical laboratory of Northwestern University Medical School upon aged or preserved human and animal blood plasmas have shown the following changes:

In the first 48 hours, an increase of ac-globulin and a corresponding shortening of the prothrombin time. On the fifth day there is a decrease of ac-globulin, a prolonged prothrombin time, and an increase of antithrombin activity.

The variations in the antithrombin activity were found to be strictly related with the variations of the pH of the plasma; that is, there was more antithrombin activity on the alkaline side. Experiments demonstrated that not only the alkalinity of the plasma increased the antithrombin activity, but that this antithrombin activity could be reduced by treating the plasmas with protamine sulphate without changing its pH. This suggests, then, that an heparin-like substance, or maybe heparin itself, acts at its optimum when the pH of the plasma is on the alkaline side.

By producing acidosis and alkalosis *in vivo* in dogs, it was found that a shift to a pH of 7.2 shortens the clotting time of recalcified plasma 100 times. This shortening was due to an increase in the activity of the ac-globulin and a decrease in the antithrombin activity of the plasmas. These variations in pH are compatible with life, and were also found in postoperative human plasmas, more frequently after prolonged anesthesia.

These results suggest that any measure to maintain the pH of the plasma during and after surgery within a normal range would prevent a thrombo-embolic tendency. Our results also support the work presented yesterday by Dr. Gibbon and his associates—that respiratory acidosis must be avoided.

It is advisable to run pH determinations of blood during and after surgery, and mechanical ventilation might be one of the best means to control respiratory acidosis.

DR. LOYAL DAVIS: My remarks are prompted by Dr. Child's paper, and although the work in our laboratory has been carried out upon dogs—and therefore my remarks are not directly applicable to his experiments with the monkey—I think that they will be of interest to you.

This work has been carried out with Dr. Thomas C. Douglass and Dr. Carlos Tanturi. In the past two years we have been making studies upon the hepatic circulation. I will not say anything now about our work on the arterial supply to the liver, but will confine my remarks to the portal side.

We found that partial reduction of the portal flow by means of a Goldblatt clamp produces the development of a portal collateral circulation in the dog, and is compatible with the life of the dog. If, after 15 to 25 days, the portal vein is then completely occluded, the animals also survive, because of this well-developed collateral circulation, and we found that treatment with penicillin increases the percentage of survival. However, sudden occlusion of the portal vein at its entrance into the liver, performed at one operation, was always fatal in dogs, even when penicillin was given, and we believe that the death is due to two main factors: First, that there is an excess loss of fluid through the intestinal wall into the abdominal cavity, and, second, that death is due to toxemia due to anaerobic infection, the source of which is in the intestine.

One out of ten dogs with a sudden ligation of the portal vein survived. The anatomic studies upon that dog showed that double ligature of the portal vein was placed below the entrance of the small superior pancreatic vein, which had been transformed into a main channel of the well developed collateral circulation and took care of all the splenic venous blood.

In the normal dog it may frequently be observed that the inferior mesenteric vein diverts its blood into the splenic vein so that more than 50 per cent of the total portal blood is carried by the splenic vein. We believe, therefore, that the survival after a sudden occlusion of the portal vein at its entrance into the liver will depend upon the rapidity of the development of the collateral circulation. Abdominal studies show that in partial occlusion of the portal vein in the dog, this takes from 15 to 25 days.

Finally, we made some studies upon portal vein pressure in dogs, with a partial occlusion of the portal vein, and it was shown that a well-developed collateral circulation is not necessarily equivalent to portal hypertension.

Dr. Hilger P. Jenkins: I would like to briefly supplement the paper by Drs. Berry and Bougas by demonstrating a case of mesenteric thrombosis with color motion pictures. The patient was a man, age 58, who was admitted to the Woodlawn Hospital with a history of upper abdominal pain which came on rather suddenly 36 hours previously. The pain was intense and continuous. He gave a previous history of abdominal distress of 15 years' duration which came on after meals and was relieved by various medications. On examination there was generalized tenderness and rigidity. The temperature was 99° F. The w.b.c. was 16,000 and the r.b.c. normal. X-ray showed no evidence of air under the diaphragm. There was very little evidence of distention of small intestine except for one loop about midway in the small intestine.

The preoperative diagnosis was perforated ulcer, possibility of internal strangulation obstruction. At emergency operation a segment of mid small intestine approximately two and one-half feet in length was found to be distended and markedly discolored. There was edema and discoloration of the mesentery to this portion of intestine. There was no evidence of any adhesion band or internal hernia which might have contributed to strangulation.

Resection of the involved bowel and anastomosis was performed. On opening the specimen the sharp line of demarcation was seen between the normal mucosa and the purple discoloration of the involved portion. On cutting through the mesentery evidence of thrombosis of the mesenteric veins could be seen. The patient was discharged on the eighth postoperative day in good condition.

In conclusion I would like to point out the negligible X-ray findings in this case as contrasted to the rather marked distention of the thrombosed segment of intestine which was found at operation, and demonstrated in the motion picture. This emphasizes again the importance of clinical diagnosis for acute abdominal disease which may or may not be supported by X-ray findings.

Dr. W. Barclay Parsons: I was very much interested in Dr. Child's presentation. For a number of years we have been very much bothered by what to do about the portal or superior mesenteric vein behind the head of the pancreas, when involved with tumor. Last August, Dr. John Lockwood and Dr. Porter did a partial resection of the vein where it was involved in extension from the posterior part of the neck. About four months ago we had the opportunity of doing a total pancreatectomy, with splenectomy, for a patient who presented herself with pancreatico-lithiasis, and evidence, by X-ray, of a non-diagnosable mass. We took a biopsy, and to our surprise and Dr. Stout's surprise, this turned out to be an epithelial, epidermoid carcinoma, presumably arising in the duct.

We went ahead with the total pancreatectomy, plus splenectomy. Everything went splendidly until the very last point, where it was quite obvious that there was extension of the tumor into the vein. We tried to do a partial resection, but that was obviously out of the question. Knowing of the two cases that Dr. Child reported this afternoon, we went ahead with an excision of a portion of the vein. The patient has done very well, and had not a particularly stormy convalescence.

I think the important point is that this particular patient had a partial obstruction to her vein. We didn't know enough to do some studies with injections, so we have

no data, unfortunately, as to the stage of the collateral circulation that she might have developed.

I am sure that—with the testimony of Dr. Davis and Dr. Child as to the great difference in the experimental animals—in the human being the only time when a partial resection of the vein is possible, with life of the patient, is in those cases where there has been partial obstruction for a long enough period (and who knows how long a piece of string is?) for the collateral circulation to have started.

DR. MICHAEL E. DE BAKEY: I, too, should like to limit my remarks to the report of Dr. Child and his associates. I should like to refer to an experience I had about a year ago with a case of mycotic aneurysm of the superior mesenteric artery. Such an occurrence is in itself unusual, but the fact that the aneurysm proved to be resectable after ligation of the superior mesenteric artery with no effect upon the viability of the bowel supplied by this vessel is, I believe, unique. Because the superior mesenteric vein was also ligated this clinical experience may be of interest in connection with the experimental observations presented by Dr. Child.

The patient was a white female, 27 years of age who four years previously had developed subacute bacterial endocarditis which was successfully treated by intensive penicillin therapy. At the time I saw her she had a slightly tender, pulsating ovoid mass about 5 cm. in diameter which was palpable in the upper abdomen just to the right of the midline. The mass could be easily moved from side to side for a distance of several centimeters. On this basis a diagnosis of mycotic aneurysm of the superior mesenteric artery was made and at operation this diagnosis was confirmed. The aneurysm was found to arise from the superior mesenteric artery just below the inferior border of the pancreas and the origin of the inferior pancreaticoduodenal artery. The main vessel was exposed and freed immediately above the aneurysm and a fine rubber tube placed around it to be used for traction and control of hemorrhage. After further dissection and exposure of the aneurysm it became apparent that a reparative procedure was improbable and excision would be necessary for cure. The collateral circulation was then tested by temporary complete occlusion of the superior mesenteric artery immediately above the aneurysm for about 20 minutes. This produced no appreciable color change in the bowel and it was therefore decided that resection was feasible. Accordingly the aneurysm was extirpated, but in carrying out the resection it became apparent that the superior mesenteric vein was so involved in the wall of the aneurysmal sac that it too would require ligation and division. Upon occlusion of the superior mesenteric vein the small bowel became moderately cyanotic in color but remained viable and the discoloration gradually improved during the time of the operation. The patient's postoperative progress was satisfactory and when last observed almost a year after the operation she was perfectly well.

I believe that this case demonstrates the fact that under certain conditions adequate collateral circulation exists to permit ligation of both the superior mesenteric vein and artery, thus lending clinical evidence in support of the experimental findings presented by Dr. Child. The arterial collateral circulation in this case was probably developed gradually as a consequence of the slowly progressive impairment of blood flow through the main channel produced by the aneurysm. I am inclined to believe, however, that the venous collateral circulation was brought into play suddenly since there seemed to be no impairment of the blood flow through the main vessel, the superior mesenteric vein, at the time of its ligation.

DR. CHARLES G. CHILD, III (in closing): I should like to point out, perhaps, one fact of interest, and that is that in the dog and cat and rabbit, the anatomic relationships of the pancreas and duodenum are those in an intramesentery position. The tract of the monkey corresponds almost identically with man, as do the pancreas and the duodenum, and in all our experiments we have been unable to detect any significant variation in these two.

VALVULOTOMY FOR THE RELIEF OF CONGENITAL VALVULAR PULMONIC STENOSIS WITH INTACT VENTRICULAR SEPTUM

REPORT OF NINETEEN OPERATIONS BY THE BROCK METHOD*

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The first attempt to treat valvular stenosis by surgery was made by Doyen in 1913 and is described by J. Dumont.[1] The patient was believed to have valvular pulmonic stenosis, and the treatment consisted of an attempt to relieve the stenosis by dividing the lesion with a small tenotomy knife which was introduced through the wall of the right ventricle. The patient survived only a few hours, and necropsy demonstrated a subvalvular rather than a valvular stenosis. No further attempts were made to treat valvular pulmonic stenosis by a direct attack on the valve itself until recently; in the intervening time more attention has been focused on the surgical treatment of mitral stenosis. The results in the 1920-30 period were rather discouraging, whereas those in the past several years have shown considerable improvement. Recent progress in the treatment of valvular pulmonic stenosis has paralleled the advance in the treatment of mitral stenosis. Russell Brock[2] reported (June 12, 1948) the results of operations on three patients in whom the stenotic pulmonary valve had been divided during the preceding four months. Holmes Sellors[3] reported (June 26, 1948) a single case in which the pulmonary valve had been divided successfully almost eight months previously. In his last published report in August, 1949, Mr. Brock[4] described the ten patients in whom pulmonary valvulotomy had been attempted. The result was excellent in two of these; in two it was considered to be moderately satisfactory, and in one the operation was too recent to permit evaluation of the result. Three of the five deaths were due to cardiac failure which occurred shortly after the chest was opened. It will be brought out later that Mr. Brock's recent experience while visiting in this country was much more favorable.

In congenital stenosis of the pulmonary valve there is fusion of the three semilunar cusps to form a domelike structure with a small central perforation (Fig. 1). During systole this diaphragm projects into the pulmonary artery and a small but powerful jet of blood is forced through the valve. It is probably this jet effect which is responsible for the poststenotic dilatation

* Aided by a Grant from the Robert Garrett Fund for the Surgical Treatment of Children and by the Gift of Mr. Hal Price Headley of Lexington, Kentucky. Read before the American Surgical Association, Colorado Springs, Colorado, April 20, 1950.

which is usually seen in this condition. In some patients the pulmonary artery is dilated to several times its normal size, assuming almost aneurysmal proportions. The pressure within the artery is, however, low rather than high. Proportional to the severity of the stenosis and to the age of the patient, there is right ventricular hypertension and secondary right ventricular and right auricular hypertrophy and dilatation.

It has been customary to refer to valvular pulmonic stenosis occurring without an interventricular septal defect as "pure" pulmonic stenosis. It should, however, be remembered that in about 70 per cent of these patients the foramen ovale has been held open by the elevated right auricular pressure; a right to left shunt is thus produced which may involve more than half of the venous return to the right auricle. This fact alters the hemodynamics of

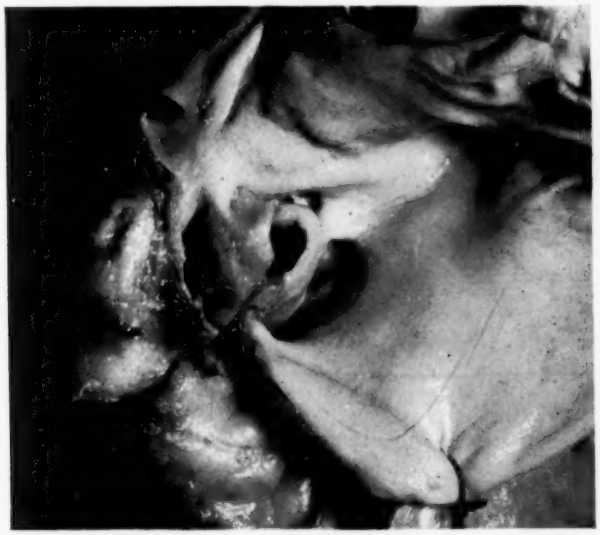


FIG. 1.—This shows the domelike structure formed by the fusion of the three cusps of the pulmonary valve. Since this valve has been cut with a valvulotome, the degree of stenosis appears less than was actually the case.

the condition in that an escape valve has been provided which to some degree decompresses the right auricle and may delay the onset of right-sided heart failure. It also introduces the factor of cyanosis and increases the left ventricular output. It is interesting to note that in one of our patients (A. V.) the mother observed that as his cyanosis increased his exercise tolerance improved. We attributed this improvement to an increase in the right to left shunt through the foramen ovale.

Valvular pulmonic stenosis in association with a patent foramen ovale can easily be confused with a tetralogy of Fallot, as in three of the patients reported herein. It is important from the viewpoints of both diagnosis and surgical therapy that one should clearly understand the anatomical and

mechanical differences between these two conditions (Figs. 2 and 3). In the majority of cases of tetralogy the stenosis is in the pulmonary conus of the right ventricle, the infundibulum, rather than in the valve itself. As pointed out by Brock, a direct attack on the stenotic infundibular region may be feasible in some of the patients with the tetralogy of Fallot, particularly those with a large infundibular chamber between the region of stenosis and the valve. This approach, however, is a much more difficult and dangerous one than the attack on the stenotic pulmonary valve. Another important

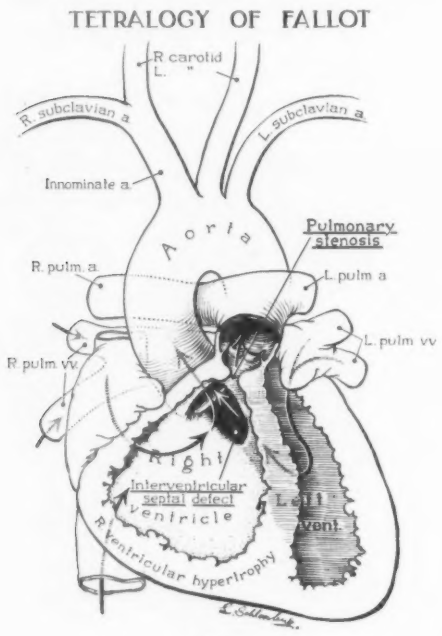


FIG. 2

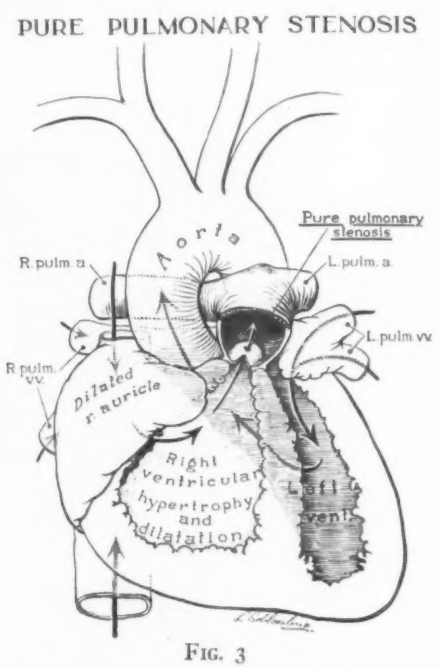


FIG. 3

FIG. 2.—Diagram of tetralogy of Fallot—note stenosis of infundibulum with the infundibular chamber lying between the point of stenosis and the essentially normal pulmonary valve. There is a high interventricular septal defect with overriding of the aorta.

FIG. 3.—Diagram of "pure" pulmonic stenosis—note fusion of valvular cusps to form diaphragmlike structure with small central perforation. The interventricular septum is intact and the main pulmonary artery beyond the valve is dilated. There is a greater degree of hypertrophy of the right ventricle and right auricle than is seen in the tetralogy of Fallot. Patency of the foramen ovale is not indicated, but is usually present.

difference between the two conditions lies in the fact that in the tetralogy of Fallot there is an interventricular septal defect with overriding of the aorta. This permits the aorta to receive blood from the right ventricle as well as the left, and constitutes an escape valve which protects the right ventricle from an excessive degree of hypertension. In such a situation the mixed blood of the left ventricle can be shunted to the lungs by an anastomosis between a systemic and a pulmonary artery, with great improvement in arterial oxygen content and relatively little danger of right-sided heart failure. How-

ever, the patient with valvular pulmonic stenosis in association with a patent foramen ovale is in a far more precarious state of balance as regards his pressure relationships. Whereas such a shunt will improve his peripheral arterial oxygen saturation, it will also increase the pulmonary venous return to the left auricle and diminish the shunt through the foramen ovale which has been decompressing the right side of the heart. Such a patient can be expected to have severe right-sided heart failure shortly after operation. It is apparent, therefore, that when pulmonic stenosis occurs without an interventricular septal defect a direct attack on the stenotic area is necessary. The presence or absence of a patent foramen ovale does not alter the nature of the surgical treatment.

No attempt will be made to consider in detail the diagnosis of valvular pulmonic stenosis without an associated interventricular defect, since this condition will be dealt with by Dr. Helen Taussig and Dr. Mary Allen Engle in another publication. All of the patients reported herein were studied by Doctor Taussig. In a number of the cases we have had the advantage of catheterization studies by Dr. Richard Bing and his associates and angiocardiographic studies by Drs. Robert Sloan and Robert Cooley (Figs. 4 and 5). Judging by the findings at operation, the preoperative diagnoses have been remarkably accurate. The more important features of the history, the physical examination, and the findings by special methods of study are listed below.

Exercise intolerance.

Cyanosis if shunt is present (70 per cent), usually late onset.

Clubbing of digits.

Enlarged, pulsating liver.

Occasional peripheral edema and ascites.

Prominence of precordium with precordial heave.

Cardiac enlargement, predominantly right-sided.

Systolic murmur and thrill.

Dilatation of main pulmonary artery visible on roentgen-ray examination.

Absence of vigorous pulsations in lungs on fluoroscopy.

Polycythemia depending on degree of unsaturation.

Albuminuria.

Prolonged circulation time, variable, depending on interauricular septal defect.

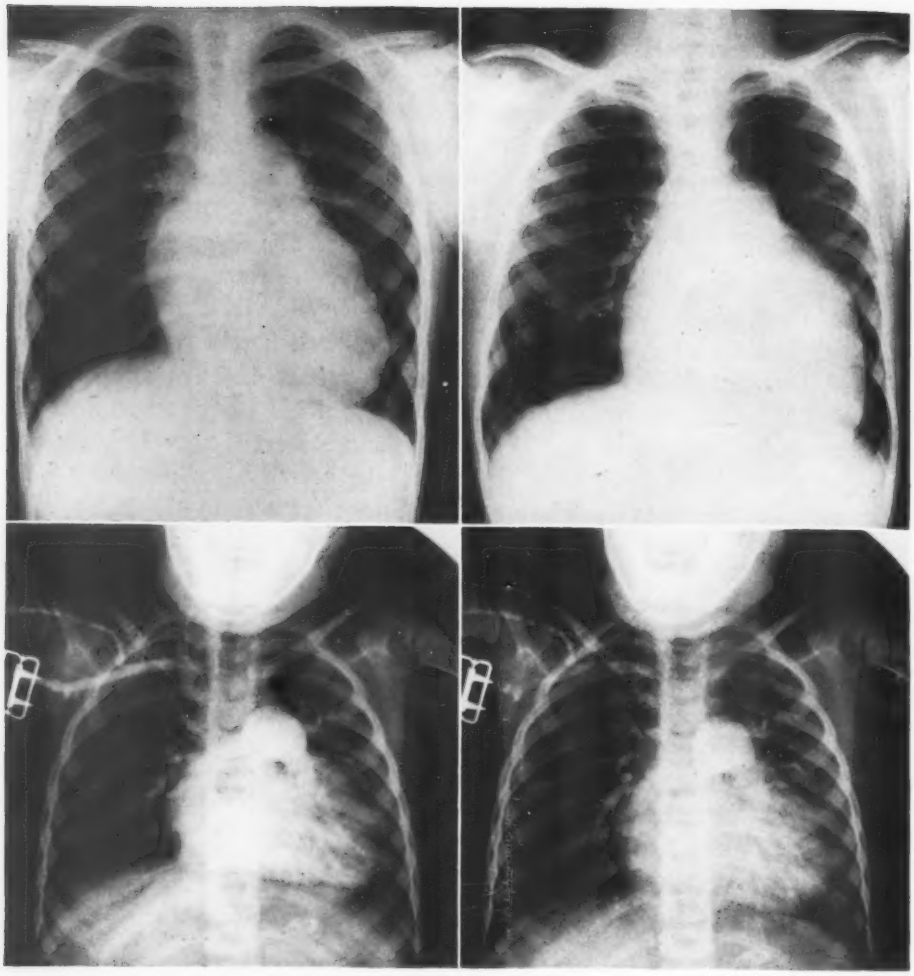
Electrocardiogram: right axis deviation and right ventricular hypertrophy early, right bundle branch block late.

Angiocardiography: slow passage of dye through heart unless there is large interauricular septal defect, large right ventricle, poststenotic dilatation of pulmonary artery with lingering of dye.

Catheterization: high pressure in right ventricle, low or normal pressure in pulmonary artery, diminished pulmonary flow, arterial oxygen unsaturation, depending on interauricular septal defect.

FIG. 4

A B



A B

FIG. 5

FIG. 4.—Chest roentgenograms of two patients (J. T. and C. B.) discussed in text—note cardiac enlargement and prominence in region of main pulmonary artery.

FIG. 5.—Angiocardiograms of patient (E. F.) discussed in text. (A) This was taken two seconds following injection of the opaque medium and shows the marked dilatation of the main pulmonary artery. (B) This was taken two seconds later and shows the opaque medium to be lingering in the pulmonary artery and still no opacification of the aorta.

It is not necessary to employ all of the special methods of study in all cases, since the correct diagnosis may become apparent from the usual clinical and radiologic examinations.

OPERATIVE PROCEDURE

The operation is that which has been described by Mr. Brock of Guy's Hospital, London, and in fact he performed the operation on seven of the patients described in this report while he was serving as an Exchange Professor in The Johns Hopkins Medical School and Hospital. Slight variations which we have made in Mr. Brock's technic are without significance.

If the patient presents evidence of heart failure, digitalis is administered preoperatively. If cardiac irregularity is found on electrocardiographic studies, quinidine is given. On the evening prior to operation, the intramuscular administration of penicillin is begun. The pre-anesthetic medication includes the giving of morphine and atropine. Blood or plasma, depending upon the degree of polycythemia, is administered continuously during the operation through a cannula inserted into a vein in the ankle. At the time the pleural cavity is entered a peripheral vasoconstrictor with a prolonged duration of action (Drinalfa in these cases) is injected intramuscularly. When the pericardium is opened procaine 1 per cent in a dosage of 2 mg. per Kg. of body weight is given intravenously and is repeated if an arrhythmia of ventricular origin develops. At the same time 5 to 10 cc. of 4 per cent procaine are instilled into the pericardial cavity and allowed to remain for about five minutes while further dissection of the pericardium is carried out. The usual cardiac stimulants, as well as an electrical defibrillator, constitute part of the routine equipment.

The anesthesia in these cases has been very capably administered by Miss Olive Berger and her staff. It has consisted of cyclopropane for the induction, followed by ether. An endotracheal tube is inserted and respirations are manually assisted throughout the entire operation. A special effort is made to keep the lung on the operated side as well inflated as is consistent with adequate exposure of the field. Occasionally the anesthesia is supplemented by small doses of curare, but this was used only infrequently in the more recent cases. The plane of anesthesia is light and the patient is usually awake at the end of the operation.

For the operation the patient is placed on his back and a left anterolateral approach is used. The incision extends from the left margin of the sternum to the midaxillary line and the pleural cavity is entered through the third intercostal space. The incision in the pleura and muscle extends further posteriorly than the skin incision. In most instances the fourth costal cartilage is removed and the internal mammary blood vessels are ligated and divided. In most of these patients the right ventricle is considerably enlarged, and this fact makes its exposure easier from the left than would otherwise be the case. A small opening is made in the pericardium just anterior to the phrenic

nerve, and after some of the fluid has been allowed to escape, procaine is injected and is left in the cavity for several minutes. During this time the fatty tissue and thymus overlying the left side of the pericardium are dissected towards the midline. A long longitudinal incision is made in the pericardium just anterior to the phrenic nerve, and by means of two transverse incisions near the ends of the longitudinal incision a flap of pericardium with its base near the midline of the sternum is created. It is possible to dislocate the heart somewhat to the left by traction on this flap of pericardium. Procaine, 4 per cent, is applied topically to the surface of the right ventricle.

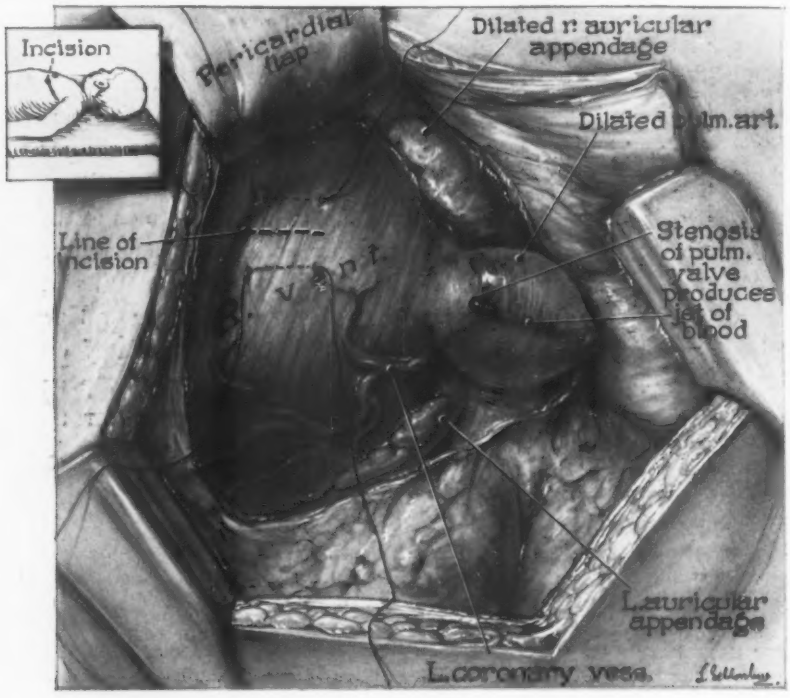


FIG. 6.—Exposure of operative field—note relation of incision to the region of the pulmonary valve and the anterior descending branch of the left coronary artery. The pulmonary artery has been made transparent to demonstrate the domelike valve and the jet of blood flowing through the small orifice.

After the pericardium has been widely opened the pulmonary artery and right ventricle and other structures are inspected and palpated. The length of time available for this examination varies; in some instances the pulse becomes poor and the blood pressure falls after the heart is exposed and one must proceed rapidly with valvulotomy. A brief examination will usually enable one to substantiate the diagnosis. The pulmonary artery in valvular stenosis is narrow at its beginning and just distally in most patients becomes a large thin-walled dilated vessel. Palpation of the first part of the dilated

pulmonary artery reveals a thrill of high-pitched frequency. The jet of blood which has passed through the stenotic valve is distinctly felt. In addition, one can usually feel by light palpation the convex surface of the dome-like shape of the stenotic valve as it is thrust forward with each systole. On palpating the region of the base of the right ventricle one does not feel the thrill that is palpable over the pulmonary artery. At the base of the pulmonary artery the bulbous distention of the sinuses of Valsalva usually is not seen and the area appears flattened.

It may be difficult to differentiate valvular and infundibular stenosis, and furthermore both types may be present. If the stenosis is infundibular rather than valvular, the thrill in the pulmonary artery is coarser and of lower frequency and is felt over a wider area, and a contraction wave can be seen

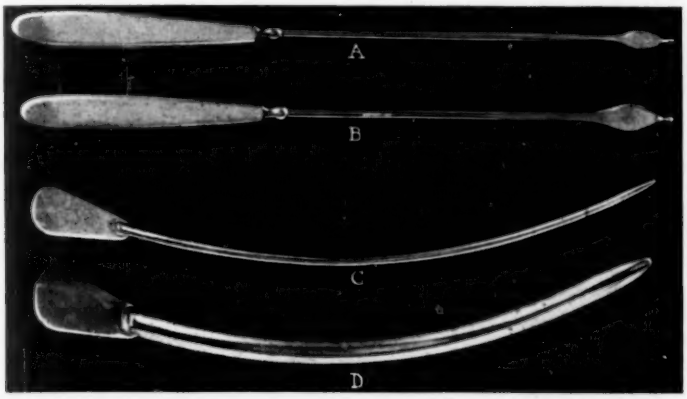


FIG. 7.—Pulmonary valvulotomes and sounds devised by Mr. Brock and Mr. Schrantz. (A) small valvulotome; (B) large valvulotome; (C) pulmonary artery probe; and (D) pulmonary artery sound.

proceeding from the infundibular chamber to the pulmonary artery. Beyond the infundibular chamber the pulmonary artery is not noticeably enlarged and the sinuses of Valsalva may be visible; also the jet effect is largely dissipated before the blood passes through the pulmonary valve. In doubtful cases pressure measurements in the right ventricle, in the pulmonary artery, and in a suspected infundibular chamber may be of help in differential diagnosis. We expect to utilize such measurements to a greater extent in the future.

If the diagnosis of valvular pulmonic stenosis is confirmed by inspection and palpation, 0.5 per cent procaine is injected into the myocardium of the right ventricle about 6 cm. caudad to the region of the pulmonary valve. Temporary irregularity of the heart may result, and a decline in blood pressure may occur, in which case one should proceed with valvulotomy as rapidly as possible. Two stay sutures are placed several centimeters apart in a longitudinal direction in the myocardium of the right ventricle at the site where the procaine had been injected (Fig. 6). An incision parallel to, and between

these sutures is made with a small sharp knife. This incision extends only partially through the ventricular wall. One may then use the instruments which were designed by Mr. Brock for location, division and dilatation of the stenotic valve. These are shown in Figure 7. The first is a curved probe with a small tip with which one may locate the cavity of the right ventricle and determine the angle at which the instrument must turn in order to enter the pulmonary artery. Furthermore, some estimate as to the degree of stenosis may be obtained by noting the resistance offered to the passage of the probe. After removal of the probe the small flat Brock valvulotome is introduced into the right ventricle with its broad surface parallel to the direc-

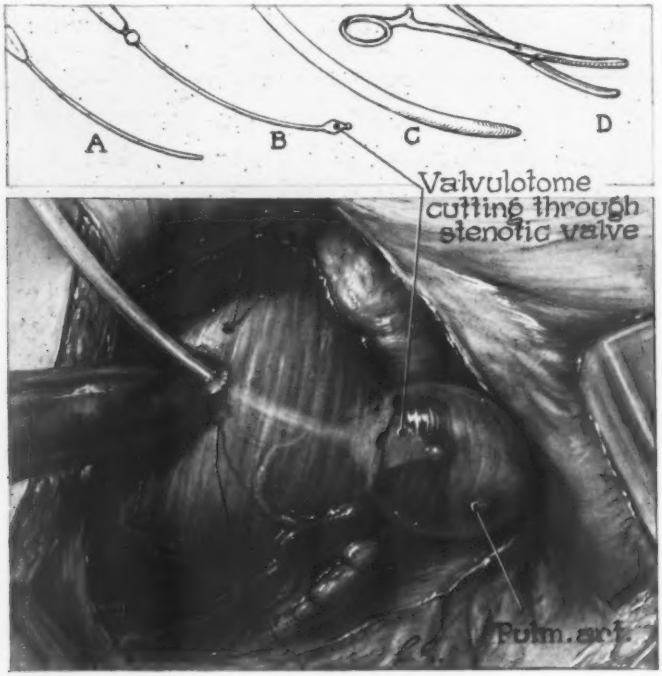


FIG. 8.—Transparency to demonstrate cutting of pulmonary valve with the flat Brock valvulotome.

tion of the incision (Fig. 8). The main secret of the success of this operation is this simple instrument.* The valvulotome has a gently curved shaft ending in a blade shaped like a spearhead with a short blunt probelike end. The two edges proximal to the probe-end are sharp and cutting and the shoulders and the retreating edges are blunt. This flat valvulotome is introduced through the incision in the right ventricle and through the stenotic valve until the probe-end can be palpated in the pulmonary artery. In most instances the resistance offered to the passage of the valvulotome is not great, since the walls

* Made by Mr. Schrantz, Genito-Urinary Manufacturing Company, 28a Devonshire Street, London, W.1, England.

of the stenotic valve are usually fairly thin and the blades of the valvulotome are sharp. Following removal of the instrument, bleeding is controlled by pressure with the index finger and slight traction on the stay sutures. A larger valvulotome is introduced, resulting in further division of the stenotic valve. At present we have a choice of valvulotomes of three sizes and propose to have others made of varying widths.

After a large cutting valvulotome has been used, a circular sound is passed with which the valve is dilated (Fig. 9). The passage of one or more sounds is followed by the introduction of a curved clamp which is opened partially at the proper place, resulting in further stretching and tearing of the valve.

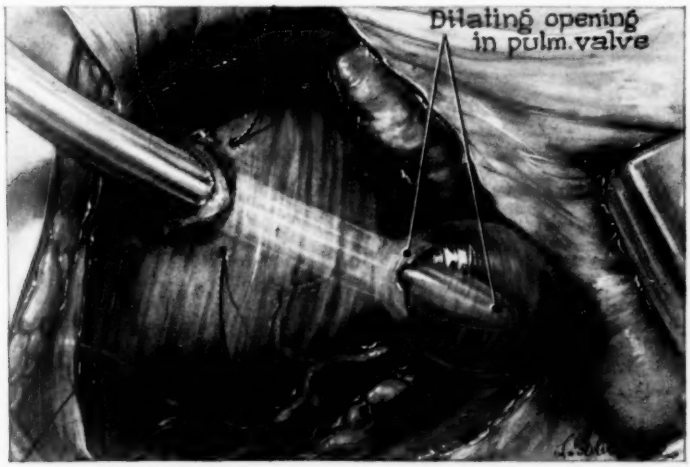


FIG. 9.—Transparency to demonstrate dilatation of previously divided pulmonary valve by passage of curved sound.

None of the valve has been removed in the operations herein reported, although it would be feasible to do so if it were considered advisable. After the desired degree of cutting and dilatation of the valve has been attained, the incision in the myocardium is closed with interrupted sutures and the stay sutures are removed. The action of the heart frequently becomes poor while the instrumentation is being carried out and the arterial pressure declines. Improvement, however, usually takes place promptly after manipulation is stopped. Palpation of the pulmonary artery then reveals a lower pitched thrill, evidence of increased pressure, and a prominence in the region of the sinuses of Valsalva which was not present before. The pericardium is loosely closed and a catheter is placed in the pleural cavity through an intercostal space. The incision in the chest wall is closed in multiple layers with interrupted sutures. The entire operating time on children is only about an hour and most of this is spent in making and closing the incision in the chest.

We wish to emphasize a point made by Mr. Brock, which is that the action of the heart may become very poor shortly after this organ is exposed.

A decline in the systemic arterial blood pressure in the presence of severe pulmonic stenosis results in definite dimunition in the flow of blood to the lungs, and the entire circulation, including that to the myocardium, suffers. Under such circumstances one should proceed immediately with division of the stenotic valve rather than wait with the hope that the action of the heart will improve spontaneously. Recently, Drinalfa has been injected intramuscularly just before the heart is exposed, and it is our impression that it has been helpful in preventing a fall in blood pressure.

PRESENTATION OF CLINICAL MATERIAL

The material in this report consists of 19 patients, all of whom underwent pulmonary valvulotomy by the Brock technic between November 1, 1949, and March 15, 1950. These patients ranged in age from 14 months to 20 years, the average age being eight years. There were 12 females and seven males. Only two of the patients gave no history of cyanosis. Five patients were noted to be cyanotic at birth, and in the remaining 12 cyanosis developed at some time between six months and five years of age. As can be seen in the table, ten of the 17 patients in whom the peripheral arterial oxygen saturation was determined preoperatively showed less than 80 per cent saturation. One of the patients in whom this determination unfortunately was not made was intensely cyanotic.

As regards exercise tolerance, all but one of these patients (M. K.) showed great limitation of activity. Most of them were able to walk one to four city blocks on level ground without resting, but three were unable to walk more than a few feet. Only five of these patients gave a history of squatting, whereas in patients with the tetralogy of Fallot this is an almost universal finding. In 17 of the patients the liver edge could be felt 1 to 6 cm. below the right costal margin and in 16 of them definite pulsations could be detected. In the one instance where there was no hepatomegaly it was our impression that the interauricular septal defect was unusually large.

All but one patient had a loud, harsh systolic murmur in the pulmonary area at the time of operation. The patient in whom no murmur was audible (A. W.) had had one when seen three months previously. Associated with the disappearance of the murmur was a deterioration in the patient's condition and a deepening of the cyanosis. At operation the findings indicated that the opening in the pulmonary valve had closed completely and that the patient's life was sustained by collateral circulation. Except in two instances, cardiac enlargement was present, and 14 patients had a cardio thoracic ratio of 60 per cent or above. In almost all instances this cardiomegaly was associated with prominence of the precordium.

As can be seen in the table, a number of these patients had some degree of polycythemia, and the increase in the number of red cells was, in a rough way, inversely proportional to the arterial oxygen saturation. On reference

to the table it can be seen that in all instances where cardiac catheterization was successfully carried out there was a significant degree of right ventricular hypertension. It is interesting that the girl (M. K.) who was found to have the highest pressure in the right ventricle (223/13 mm. mercury) was the only patient in whom there was no serious impairment in exercise tolerance. She was able to carry on a normal but quiet way of life and could walk about one mile on level ground. Radiologic studies in these patients consistently revealed diminished vascularity of the lung fields, right-sided enlargement of the heart, and marked prominence of the main pulmonary artery. The electrocardiogram in two instances demonstrated a right bundle branch block. The other tests showed right axis deviation with patterns suggestive of right auricular and right ventricular hypertrophy.

It is a tribute to Doctor Taussig and her group that in each case the preoperative diagnosis proved to be correct. Three of the patients, however, had previously been thought to have the tetralogy of Fallot and had had an artificial ductus created. Two of these patients had been operated on in The Johns Hopkins Hospital more than two years previously and had been in severe right-sided heart failure since shortly after the operation. In the other patient an anastomosis had been performed in another hospital six weeks prior to valvulotomy and prompt and severe failure had developed.

During operation all these patients demonstrated a rather constant pattern of behavior. Until the valve was divided they were in a precarious state, when, as has been emphasized by Brock, any undue delay while awaiting improvement in the patient's condition might well have proved fatal. There was sometimes a transient decline in blood pressure during anesthesia; in each case the systolic pressure fell 20 to 60 mm. of mercury at the time the pericardium was opened and in four instances the pressure became inaudible. However, with expeditious division of the valve, the heart action usually improved promptly and the pressure returned to the preoperative levels. This fact was most strikingly demonstrated in the patient who had no murmur at the time of operation (A. W.). She was intensely cyanotic from the outset of the operation, and by the time the pericardium was incised her blood pressure was unobtainable and the heart action was very weak. By the time the first instrument was passed the contractions were scarcely perceptible. Within one minute following division of the valve the heart showed vigorous, forceful contractions and the blood was a normal red. Another patient survived two brief periods of cardiac arrest. Aside from extrasystoles caused by manipulation of the heart, no arrhythmias were noted.

Postoperatively the patients were kept in an oxygen tent for about 48 hours and careful attention was paid to fluid balance. In patients who had been digitalized preoperatively, digitalis was continued for a week or two after operation and then discontinued. One patient (E. W.) who had been in severe failure following creation of an artificial ductus two years previously and who required a second procedure to close the ductus, was discharged

from the hospital on a maintenance dose of digitalis. All patients were given prophylactic doses of penicillin for ten days postoperatively. It is interesting that for five to ten days after operation these patients had an elevation of temperature of greater degree than one might expect. It was thought that this might have been related to the myocardial damage produced by the incision in the right ventricle. The patients were kept in the hospital for three weeks and were allowed to get out of bed during the last week.

There have been two deaths in this series of 19 cases. The first occurred in the first operation in this series in a 14-year-old boy (H. W.) who had been operated on about two and one-half years previously with the diagnosis of tetralogy of Fallot; an artificial ductus had been created on the left side. About two weeks after operation signs of right-sided heart failure appeared. Since then he had been maintained on digitalis and had been virtually confined to bed. He was in very poor condition with extreme cardiac enlargement, a large pulsating liver, auricular fibrillation, peripheral edema, and three plus albuminuria. Except for a severe fall in blood pressure he tolerated valvulotomy fairly well. It was then felt advisable to attempt closure of the artificial ductus. Shortly after this dissection was undertaken his heart action became very weak and finally ceased. It was revived with adrenalin and massage but could not be maintained, and the patient died on the operating table. At autopsy the pulmonary valve was found to have been divided. Since then there have been two other patients who previously had creation of an artificial ductus. In one of these patients the anastomosis was successfully closed at the time of valvulotomy and in the other the anastomosis was closed two weeks subsequent to the valvulotomy. The latter of these two patients remained in severe failure with a large pulsating liver after valvulotomy, but made rapid improvement after closure of the anastomosis.

The second death occurred in a 9-year-old girl (J. T.), the eighth patient in this series, who had a severe degree of stenosis accompanied by intense cyanosis and right ventricular hypertension (see Table I). She tolerated the operation well and immediately her color was excellent and the liver pulsations were strikingly diminished. Forty-eight hours after operation following several hours of restlessness and mental confusion she suddenly became comatose and voluntary respiratory effort ceased. Artificial respiration was maintained through an endotracheal airway, and the patient was again taken to the operating room where a trephine was carried out by Dr. Robert Fisher and a left frontal lobe abscess was drained. After this procedure the child was kept in a respirator, but pursued a progressively downhill course, dying about 72 hours after the valvulotomy. Autopsy again demonstrated successful division of the pulmonary valve as well as a chronic brain abscess of the left frontal lobe. For several weeks before coming to the hospital the child had had mild recurrent headaches and on admission there was leukocytosis (15,000 wbc/c.mm.). The significance of these symptoms, however, was not appreciated, and the presence of a brain abscess was not suspected. Except

for this previously existing abscess, she would almost certainly have been greatly benefited.

The other 17 patients are alive and in good condition. It is gratifying that there has been no serious postoperative complication in these cases. All the patients who were cyanotic preoperatively showed an improvement in color immediately following valvulotomy, and in several patients who had been intensely cyanotic the color promptly became normal. It is interesting that on the second or third postoperative day, particularly during exertion such as coughing or crying, the cyanotic hue sometimes re-appeared, usually to a lesser degree than before, and then subsided slowly over a period of several

TABLE I.—*Data Relative to Patients Discussed in Text.*

Patient	Age—Years	Cardio-thoracic Ratio Per cent	Red Cell Count millions/c.mm.	Right Ventricular Pressure mm./mercury	Preoperative Arterial Oxygen Saturation Per cent	Postoperative Arterial Oxygen Saturation Per cent
H.W. ♂	14	64	8.4	.....	72.8	Deceased
C.S. ♀	7	70	6.9	162/45	68.0	95.7
A.V. ♂	7	72	8.8	125/0	70.0	94.5
R.F. ♀	5	45	7.4	98/?	62.0	88.0
C.S. ♂	14	40	5.1	122/30	87.0	97.3
E.W. ♂	9	63	5.2	.....	82.1	....
T.S. ♂	1–2/12	..	8.9	85/?	....	....
J.T. ♀	9	62	7.3	191/30	76.0	Deceased
R.H. ♂	20	70	9.0	150+/?	68.0	91.4
C.B. ♂	13	62	5.5	143/0	95.6	92.4
E.F. ♀	4	57	5.3	165/36	92.3	94.5
A.W. ♀	2	63	11.8	.....	....	85.0
E.K. ♀	6	65	6.5	146/48	65.8	88.0
E.B. ♀	2	60	6.6	.....	66.0	82.0
M.K. ♀	13	60	5.2	223/13	93.5	89.4
C.J. ♀	11	60	6.3	.....	85.0	92.3
E.S. ♀	7	64	5.8	166/26	83.6	94.0
S.L. ♀	1–3/12	70	5.6	84/60	71.0	88.7
R.B. ♀	7	53	5.5	200/?	78.0	85.5

hours. As can be seen in the table a number of the patients showed a definite rise in the arterial oxygen saturation and in several this became normal.

Another striking change which was detected immediately after operation was the alteration in the character of the murmur. The original loud, high-pitched systolic murmur was usually converted into a low-pitched rumble which at times was very soft and no longer accompanied by a thrill. Liver pulsations also promptly diminished or disappeared. Only two patients at the time of discharge were believed to have faint pulsations in the liver, whereas all but one had demonstrated this sign preoperatively. After valvulotomy the size of the liver fluctuated considerably from day to day, but the general trend was a slow diminution in size. In two patients during the early postoperative period the liver edge was felt to be lower than it was preoperatively, but by the time of discharge the liver was smaller than it had been on admission. Where there had been polycythemia there was a return to more nearly normal

levels, but the validity of this observation is open to question because of the factor of blood loss at operation. Ten patients had had albuminuria on admission but this condition had cleared in nine by the time they left the hospital. The electrocardiogram showed no significant change during the observation period.

As regards exercise tolerance, it is difficult to assess improvement accurately because all of the patients are still on restricted activity. However, five of the patients had shown a high degree of exercise intolerance, and even during the period of hospitalization it was obvious that their capacity for physical activity had improved satisfactorily.

Four of these patients have recently returned to the Cardiac Clinic of the Harriet Lane Home for examination four months after operation. One of them (C. S.♀) had gained 21 pounds in weight and tolerated all allowed exercise without any sign of dyspnea or fatigue. Her red blood count had dropped about one million from the preoperative level and her cardiothoracic ratio had declined from 70 per cent to 60 per cent. Another child (A. V.) likewise had an excellent color and his mother was having difficulty in restraining his activity. His red blood count had fallen from 8.8 million per c.mm. to 4.7 million and his cardiothoracic ratio had fallen from 72 per cent to 61 per cent. In the other two patients the results were less striking because their original disability had been less severe. Both of them had a good color, but one of them (R. F.) is said still to have occasional periods of cyanosis though this was not apparent at the clinic. Neither had been active enough to determine his exercise tolerance, though one (C. S.♂) had walked as far as one mile, having been able to walk only one-half block preoperatively. These patients were placed on unrestricted activity except for C. S.♂, in whom the heart sounds were not of good quality although there was no other evidence of cardiac difficulty. He was advised to remain on restricted activity for another three-month period.

The most objective method for determining improvement would be to repeat cardiac catheterization in those patients for whom we have preoperative data. It is felt that it is still too soon after operation to carry out these studies, but they are planned for the future.

DISCUSSION

Technically this operation is not a difficult procedure. Its success depends on careful attention to detail from the beginning of the diagnostic work-up until the patient has passed through the immediate postoperative period. Much responsibility rests upon the anesthetist, who should observe the condition of the patient with particular care as soon as the chest has been opened. There may be nothing specific in the various medications which are administered both before and during operation, but we feel that each drug in its proper place fulfills a definite function.

One essential which should be stressed is adequate exposure, and this can usually be obtained by the left anterolateral approach described above, especially if the heart is enlarged. This exposure is necessary not only for instrumentation but also for adequate assessment of the situation by direct vision and palpation. While it is true that the typical case can be accurately diagnosed by preoperative studies, there will probably be many cases where the mode of treatment will depend to a large degree on operative findings. It is of the utmost importance that the various valvulotomes and probes be passed well into the pulmonary artery, because it is possible to push the diaphragmatic valve in front of the instrument for a short distance into the artery without actually dividing the valve. Usually one is aware of a sudden release in resistance as the valve gives way, but it is well to check the position of the instrument by palpating the artery beyond the valve. Also it should be borne in mind that the stay sutures function only as guides and should not be subjected to strong traction lest they be torn loose. Bleeding is best controlled by pressure with the finger. Blood loss is not likely to be great if the ventricular wall is very hypertrophic. If, however, the myocardium has been thinned out by dilatation, hemorrhage may be troublesome and require rapid replacement of blood.

One of the most interesting anatomical features of these cases, as has been commented upon above, has been the regular occurrence of marked dilatation of the main pulmonary artery just beyond the stenotic valve. At times this has attained impressive proportions and occasionally the artery has been three or four times greater in diameter than normal. This is an important diagnostic sign both radiologically and at the time of operation when the artery is exposed. Such dilatation of an artery beyond an obstruction is a well-known phenomenon which has been recognized for many years, particularly where it occurs in the subclavian artery distal to a cervical rib or in the aorta below a coarctation. Doctor Halsted[5] studied this problem in experimentally produced constrictions of the aorta and found that a considerable degree of stenosis was necessary to produce a significant dilatation of the distal portion of the vessel. He also noted an elevation of diastolic pressure and lowering of systolic pressure beyond the constriction. He felt that this lowering of the pulse pressure and the abnormal play of the blood stream produced by the powerful jet were the chief mechanical factors responsible for the dilatation. In our cases where the dilatation was very great it will be of interest to see what the ultimate fate of the artery will be. Once the valve has been divided the jet effect is largely abolished, but the artery appears even larger once it is subjected to increased intraluminal pressure. So far there has been no indication that this vessel will not function efficiently after valvulotomy.

A number of important problems present themselves in regard to this operation, some of which cannot be answered with assurance at the present time. One of the most pressing of these problems is the ultimate fate of the

incised valve. Is there any danger that the cut edges will heal together, or will the contraction of scar tissue lead to the reformation of a constriction? Also it is pertinent to ask whether or not this procedure creates an incompetent pulmonary valve which might eventually result in a serious degree of pulmonary insufficiency. It must be remembered that this operation does not merely produce a dilatation of the stenotic valve but is designed to actually divide the valve through its transverse axis from one side of the ring to the other. In such a clean surgical wound one would expect endothelialization of the cut edges to take place within a few days. On the basis of a four-month period of postoperative observation we can say only that thus far there has been no evidence of reformation of the obstruction. It is possible in the future it will be found that mere division of the valve is not adequate and that it will be desirable to actually remove a portion of the valve. Such a defect would be expected to produce some degree of pulmonary insufficiency, but in the absence of pulmonary disease producing pulmonary hypertension it does not seem likely that the valvular incompetence would be attended by dangerous consequences. Powers and Bowie[6] in 1933 excised segments of the pulmonary valve in two dogs in which a pulmonary stenosis had previously been experimentally produced. Diastolic murmurs developed but the dogs survived for 20 months without sign of decompensation. In our series of cases there has been no auscultatory evidence of pulmonary insufficiency. Moreover, in the autopsy specimens of the two patients who died the divided diaphragm looked as though it might well function as a reasonably competent bicuspid valve.

Another question which comes to mind is the fate of the interauricular septal defect which is an associated finding in most of these cases. At the present time there is not enough available information from autopsies to speak accurately about this point. It is believed, however, largely on the basis of catheterization data, that in most instances the shunt takes place through the foramen ovale which has been held open preoperatively by the abnormal pressure gradient between the two auricles. The surgical correction of the obstruction at the pulmonary valve undoubtedly reduces this pressure gradient and in some cases may bring about either functional or anatomical closure of the foramen. In some instances the defect is undoubtedly too large to allow spontaneous closure. These patients (such as R. F.) may continue to have brief periods of cyanosis when engaged in strenuous exercise. Also it is possible that there might eventually be a reversal of the shunt through the defect, the flow being from left to right as is the case when an interauricular septal defect occurs as an isolated anomaly. Such a situation would place an additional burden on the right side of the heart.

One also wonders about the effect of pulmonary valvulotomy on the size of the enlarged heart. It is the opinion of Doctor Taussig[7] that the amount of enlargement of the cardiac silhouette which is due to right ventricular dilatation can be expected to decrease promptly, but she looks upon the

myocardial hypertrophy as a more or less permanent feature. When pulmonary stenosis is relieved at an early age, the child may "grow into the size of his heart" and the cardiothoracic ratio will become more nearly normal. In several of the patients in our series a significant decline in the cardiothoracic ratio was noted four months postoperatively. It is likely that much of this reduction has taken place in the right auricular salient of the cardiac silhouette.

As has been shown by Sellers and by Brock and, as we believe, has been demonstrated by this series of cases, surgical division of the congenitally stenotic pulmonary valve is a technically feasible procedure. The mortality rate is not prohibitive when one considers the poor prognosis of the patient in whom a severe degree of stenosis exists. But when one is asked to evaluate such a patient for operation, he is faced with serious problems. What is the optimal age for such an operation? Will the opening which is created in the pulmonary valve of a young child still be adequate when the patient is full grown? Is there any basis for expecting that this orifice will enlarge as the child develops? So far this decision has not been difficult to make because most of our patients have been in such precarious condition that a prolonged delay in operation was believed to be unwarranted. Also, of course, it is desirable that the obstruction be relieved at an early age before severe and perhaps irreversible damage has been done to the myocardium, pulmonary artery, liver, and kidneys. Again we must wait on time and careful follow-up studies to solve these problems.

Congenital valvular pulmonic stenosis with intact ventricular septal defect is of less frequent incidence than our recent experience would indicate. Some of these patients had been seen previously in the Cardiac Clinic and operation had been postponed. It is Doctor Taussig's present impression that the incidence of valvular pulmonic stenosis is about one-tenth as great as that of the tetralogy of Fallot.

SUMMARY

Division of the stenotic pulmonary valve by the method of Brock has been performed on 19 patients in The Johns Hopkins Hospital in the treatment of congenital valvular pulmonic stenosis with intact ventricular septum. There have been two deaths, one attributable to severe heart failure and one due to a pre-existing abscess of the brain. The remaining patients are improved and some appear to be in normal health. There have been no deaths during or following the last 11 operations. Valvular pulmonic stenosis is a mechanical disorder which can be diagnosed by available methods of study and which can be treated by direct operative attack on the valve.

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Discussion.—Dr. Willis J. Potts: That was a very fascinating presentation of a new method for approaching a certain type of patient with congenital heart disease.

The so-called pure pulmonary stenosis often is not a single lesion, as the name implies, but is associated with an atrial septal defect. This condition accounts for a small but important group of cyanotic or very slightly cyanotic children. The degree of cyanosis is dependent upon the size of the inter-auricular defect. It is obvious, as Dr. Blalock has pointed out, that a shunt operation is contraindicated in such patients. Brock's approach is entirely logical.

[Slide] This demonstrates—as did Dr. Blalock's picture—the typical picture of so-called pure pulmonary stenosis. Looking in the pulmonary artery toward the heart, one sees the conelike constriction of the pulmonary valves. The stenotic structure projecting into the pulmonary artery resembles an infantile cervix extending into the vagina.

[Slide] In preparation for operation on such a patient, we devised a knife to open this constriction. The blade of the best cataract knife available was soldered to a rounded shaft of such size that it will fill the hole made in the ventricle by the blade. The snug fit of this shaft in the heart muscle prevents loss of blood. The rest of the handle of the knife is standard, for secure handling.

Two patients with isolated pulmonary stenosis have been operated upon with this instrument. The first child, 23 days old, weighed seven pounds, and was operated upon in December, 1949. The infant was mildly cyanotic, had some enlargement of the heart, and could not live outside an oxygen tent. From our experimental work on dogs, we planned an approach to the stricture through the pulmonary artery, but at operation on this child, the transventricular approach seemed more feasible.

[Slide] The heart was exposed through a curved submammary incision. The heart was lifted from the pericardial sac, and two holding sutures were put in the wall of the right ventricle, relatively near the base of the heart. The knife was then thrust into the right ventricle and directed toward the pulmonary artery, with the sharp edge of the blade directed toward the lumen. The constriction was cut by three radial incisions from the periphery inward. The knife was withdrawn and the wound in the ventricle closed with one stitch. The child made a rather spectacular recovery, and is doing well today, after four months.

The second child was 14 months old, moderately cyanotic, and subject to frequent attacks of unconsciousness. A similar operation was done on this child about two weeks ago. Immediately after the constriction was cut, pressure in the pulmonary artery was palpably higher. The child's color improved on the operating table, and has remained good thus far—only two weeks.

As you see in the illustration, there was some constriction of the walls of the pulmonary artery where it emerges from the heart.

The knife described worked well in these two infants. In older children with this deformity, Brock's double-bladed knife or some modification of it would be better.

DR. CHARLES P. BAILEY: Until recently the names of only two great surgeons have properly been associated with operations for congenital pulmonary stenosis. Today you see the name of Mr. Russell Brock added to those of Dr. Blalock and Dr. Potts.

At the kind invitation of Dr. Blalock, we have had the opportunity of observing him and Mr. Brock perform these operations upon the stenotic pulmonary valve. Since then we believe we have had no case of pure pulmonic stenosis. However, we have operated by this technic upon six cases of typical tetralogy of Fallot—the common garden variety of "blue baby." In three of these the stenosis was in the pulmonary valve.

The diagnosis was made at surgery, and the valve was cut in the manner so graphically shown—into a bicuspid valve, presumably without regurgitation. The children all did well, and the pressures in the pulmonary artery, taken at operation, increased from an average of 17 over 7 mm. of mercury to an average of 34 over 15. All of those children have lost their cyanosis, and their arterial-oxygen saturation is above 90 per cent.

In the other three cases the pulmonic valve and artery were normal, except for dilatation, and there was an infundibular chamber.

[Slide] That shows, of course, the typical division of the pulmonic valve into the bicuspid valve.

[Slide] On the right you see the typical stenosis of the pulmonary valve. On the left, however, you see the normal valve, but below it is a constriction. There is, in this case, a small infundibular chamber.

[Slide] These are modifications of Mr. Brock's punches, which are supposed to punch out a portion of this infundibular chamber, and that is the technic he recommends.

[Slide] Well, as it happened, in each of our three cases we cut down on the right ventricle directly over the infundibular septum, which made it impossible to use the punches, which must be put in either above or below the septum. Therefore, we did not do anything effective on the first case, and the child is still cyanotic, and only slightly improved.

In the other two cases, however, we had thought the matter over, and my associate, Dr. Robert Glover, suggested that a pair of rongeurs could be inserted through the right ventricular incision, and that a window could be made in the anterior portion of this infundibular septum. We therefore prepared a special pair of rongeurs, with tapering, streamlined jaws. In the next two cases we used this instrument, which effectively tamponaded the incision in the myocardium and removed a sizable piece of the infundibular septum. In each case we accomplished a result comparable to the three with the valvular stenosis. Both of those children have lost their cyanosis completely, and their high red blood counts have dropped to normal levels.

We have therefore performed six of these operations in regular tetralogy of Fallot, with five good results and no mortality. Now, of course, there is still an overriding aorta and a high interventricular septal defect in each instance. However, the blood flow from the right ventricle will undoubtedly continue to follow the line of least resistance into the low pressure pulmonary vessels, rather than into the high pressure aorta or left ventricle. We believe, therefore, that this procedure may be of value in certain types of tetralogy of Fallot.

DR. CONRAD R. LAM: My remarks will relate only to the selection of cases for operation, and to point out that there is probably a fairly good sized group of candidates for this operation, and that is those children who have had ill-advised shunt operations.

In approximately 100 cases with shunt operations, we have made this error three times. The first patient was a girl of 12 who had such a good result after the operation, as far as relief of cyanosis was concerned, that she was selected for a brochure prepared by the Michigan Crippled Children's Commission as a perfectly typical good result. It was not until 12 months later that she developed ascites, and the picture of constrictive pericarditis was so typical that my colleagues finally convinced me that

we might have initiated such a process. She did not survive exploration, and the autopsy showed pure pulmonic valvular stenosis, and no interventricular septal defect. Another patient who died has been reported. (J. Thoracic Surg., **18**: 661, 1949.)

The third patient showed very early congestive failure and this time the trouble was recognized. The child was taken to Baltimore, and Mr. Brock and Dr. Blalock operated on him, doing the valvulotomy and taking down the anastomosis, and he is now perfectly well.

Dr. Alfred Blalock (in closing): In regard to the diagnosis of valvular pulmonic stenosis without an interventricular septal defect I neglected to say that most of these patients have an enlarged liver which pulsates, and that the cardiac thoracic ratio is in excess of 60 per cent. Following successful valvulotomy the liver decreases in size, the pulsations disappear and the cardiac thoracic ratio decreases.

It is sometimes impossible preoperatively to tell with certainty whether one is dealing with the tetralogy of Fallot or with valvular pulmonic stenosis. In such cases one should palpate in the region of the pulmonary valve after opening the pericardium and in the presence of valvular stenosis one may be able actually to palpate the dome-shaped valve. Furthermore, one may be able to feel the jet of blood as it strikes the pulmonary artery distal to the stenotic valve.

Mr. Brock has operated upon a few patients with infundibular stenosis by a direct attack on the stenotic area. Our experience indicates that the direct attack on infundibular stenosis is much more difficult and probably much less satisfactory than the direct attack on valvular pulmonic stenosis. Some patients with infundibular stenosis have a narrow long area of constriction and it is difficult if not impossible to treat them satisfactorily by the blind direct attack. Furthermore, there is great likelihood that future scarring would result in a return of the constriction. There are probably some patients with a fairly large infundibular chamber and a narrow area of infundibular stenosis in which the direct attack will be effective. Patients with the tetralogy of Fallot rarely have valvular pulmonic stenosis, and even when such is present there may be an associated infundibular stenosis. The discussion of Drs. Potts, Bailey and Lam is appreciated.

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RESECTION OF THE AURICULAR APPENDAGES*

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RESECTION OF THE AURICULAR APPENDAGES has been proposed as a means of preventing recurrent arterial embolism in patients with rheumatic heart disease and auricular fibrillation.[8] This procedure was suggested by the frequent demonstration at autopsy of mural thrombi in the auricles of such patients who had rheumatic heart disease and auricular fibrillation and by the frequency of pulmonary and peripheral embolism. Weiss[11] stated that "rheumatic heart disease, more than any other type of heart disease, is responsible for embolic manifestations."

The incidence of mural thrombi in rheumatic heart disease increases significantly with persistent auricular fibrillation. In examining 116 cases of rheumatic heart disease, Garvin[3] found mural thrombi in 37 (31.9 per cent). Twenty-six (43.3 per cent) of the 60 patients in whom auricular fibrillation had occurred were found to have mural thrombi and 86.5 per cent of the thrombi arose in the atria (Tables I and II).

In another report, Garvin[4] recorded that in cases in which thrombi were present in the left side of the heart, 48.7 per cent showed one or more infarcts in the brain, kidneys, spleen, intestines, and/or extremities. In those with thrombi in the right side of the heart, pulmonary infarcts were found in 56.5 per cent and in left-sided thrombi peripheral infarcts occurred in 50 per cent of the cases.

Intracardiac thrombi were recorded in 22 of 30 cases by Stone and Feil[10] and in 11 of 14 by Graef and his associates.[5] The latter authors reported that in no instance was a thrombus found in the chamber of the auricle proper and that the left auricle was uniformly affected more severely than the right. Thus the auricles, and particularly the left, harbor mural thrombi in the majority of cases (Table II).

The age of the patient as well as the presence of auricular fibrillation appears to have direct influence upon mural thrombus formation. Mural thrombi have been found to occur more often in older patients.[3]

The need for prevention has been stressed by the relatively unsatisfactory results of treatment of peripheral embolus. Frequently the embolus lodges in

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a portion of the arterial bed where surgical intervention is not feasible, and even in those cases in which embolectomy can be undertaken, morbidity and mortality have been high. In several large series,[9] mortality has ranged from 40 to 59 per cent, and amputation because of resulting gangrene has been required in 18 to 22 per cent. In only 22 to 37 per cent of these cases has good circulation been restored. Once a peripheral embolus has occurred, recurrent emboli are not infrequent and are all too often fatal.

TABLE I.—*Occurrence of Mural Thrombi in R. H. D.*

		No. of Hearts	Thrombi	Percent
Graef[5]	Total	178	24	13.5
	With AF	14	11	78.5
Garvin[3]	Total	116	37	31.9
	With AF	60	26	43.3
Stone[10]	Total	100	37	37
	With AF	30	22	73.4
Hay[6]	Total	186	63	33.9
	With AF	106	52	49

The serious nature of embolic manifestations in rheumatic heart disease has been emphasized by Weiss and Davis[11] in a study of 474 autopsied cases. In 164 of these, heart disease was the cause of death. Of this group 73 (45 per cent) showed visceral or pulmonary infarcts of single or multiple organs. Embolism was felt to cause or contribute to death in 44 cases, or 26.8 per cent, of the 164 autopsies.

The feasibility of resection of the atrial appendages has been studied experimentally.[1, 2, 7] It has been demonstrated in experimental animals that the

TABLE II.—*Location of Mural Thrombi in R. H. D.*

	Ventricles			Auricles		
	Left	Right	Bilateral	Left	Right	Bilateral
Graef[5]	..	..	..	14	5	5
Garvin[3]	1	3	1	13	12	7
Stone[10]	2	4	..	19	16	..

auricular appendage can be removed without interruption of the normal heart action, with prolonged survival and with complete endothelialization at the site of removal. There does not appear to be any tendency for thrombus formation at the site of suture.

In 1949 Madden[8] reported two cases in which the left auricular appendage was removed. Both patients had rheumatic heart disease with mitral insufficiency and stenosis and persistent fibrillation, and had suffered embolic phenomena. One patient died of undetermined causes one week following operation. The other patient was found to have a left hemiparesis immediately after operation, which showed progressive improvement during the eight months follow-up period reported. These cases demonstrated that auricular

appendectomy was feasible in the human being. Stimulated by this report, the authors undertook the following cases:

Case 1.—R. B., a 50-year-old white male, was admitted July 11, 1949, to Wadsworth General Hospital, complaining of lower abdominal pain of one week's duration. The patient gave a history of "heart trouble" of approximately 12 years' duration, beginning with a coronary occlusion in 1938, for which he was hospitalized for 3 months. During the succeeding years, he was under medical observation but was relatively symptom free, save for mild substernal discomfort on exertion and occasional ankle edema.

One week prior to admission, while walking, the patient had sudden severe pain in the lower abdomen resulting in syncope. Nausea and vomiting associated with diarrhea followed, lasting 3 days but without melena. The abdominal pain persisted and increased somewhat in severity. Examination revealed a well-nourished and developed, chronically ill appearing, white male. Blood pressure 130/90, pulse 68 and irregular. Neck veins were slightly distended. Lower two-thirds of the right chest were dull to percussion anteriorly and posteriorly; occasional sibilant râles were noted in the left base and moist râles were present over the right base. Cardiac dullness extended to the left anterior axillary line in the sixth interspace. Abdomen was tender to palpation in the right lower quadrant with muscle guarding. The liver edge was 3 cm. below the costal margin. There was one plus ankle edema.

Laboratory. Hemoglobin and red blood cell count were normal; white blood count 14,200. Corrected sedimentation rate was 16 mm/hr., serology negative. Stools were negative for occult and gross blood. Blood urea nitrogen 16 mg. per 100 cc. Roentgenogram of chest, July 12, 1949, showed increased density over the right lower lung fields, interpreted as pleural effusion. Plain film of the abdomen was negative. Fluoroscopy, July 20, with barium swallow, indicated mitralization of heart. Electrocardiogram demonstrated auricular fibrillation.

Course. The patient improved with digitoxin, mercuhydrin, and a low salt diet; however, on July 22, 1949, he complained of sudden pain in the left leg associated with pallor of the left lower extremity and absent popliteal and tibial pulsations. A left femoral embolectomy was performed 3 hours later without evidence of return of circulation to the extremity. A similar episode involving the right lower extremity occurred July 31, and right femoral embolectomy was performed five and a half hours later. This leg also remained cold and cyanotic. Three days after the second operation the patient developed numbness in the left arm lasting 48 hours but without demonstrable diminution of radial pulsations. Digitoxin dosage was increased and the patient's legs were refrigerated. Slowing of pulse followed this treatment.

On August 9, 1949, left auricular appendectomy was performed. After the heart was exposed the left auricle seemed to contain a thrombus, but following amputation of the auricle, thrombus formation was absent to gross inspection. The pathologic report, however, was "old and recent organizing mural thrombi, left auricular appendage; myocardial degeneration; thickening and fibrinoid degeneration of endocardium." He received oxygen for 3 days after operation.

The patient made a satisfactory recovery. On August 26 bilateral mid-thigh amputations were performed. The patient withstood this well but developed a superficial slough of the skin flaps of the left stump. On August 31 a thoracentesis was performed, 400 cc. of serosanguineous fluid being removed. Approximately 6 weeks after operation, the patient had an episode of congestive heart failure, from which he recovered, but he has had no evidence of further embolic episodes now more than 8 months after operation. He is maintained on 1 to 2 injections of mercuhydrin weekly and a salt free diet.

Case 2.—W. D., a 63-year-old, white, unemployed male was admitted Nov. 5, 1949, complaining of right chest pain and bloody sputum of two days duration.

The patient had developed a mild non-productive cough one week earlier and had noted mild dyspnea. Two days before admission, 5 hours after his evening meal, he developed a paroxysm of coughing productive of bright red blood. This was accompanied by left parasternal pain radiating to the left shoulder. The pain continued intermittently, and he had repeated small hemoptyses. There has been no ankle edema.

The patient gave a long history of rheumatic heart disease with mitral stenosis and auricular fibrillation. He was hospitalized first in 1941 for similar symptoms and a diagnosis of pulmonary infarction made. In 1947 he was admitted with hemoptysis and transient left hemiparesis which responded to conservative therapy. In April, 1949, an episode of mild congestive failure required hospitalization. He has since been in the Domiciliary Unit of the V. A. Center, where he has received a low salt diet, 0.1 mg. digitoxin daily.

Physical Examination. The patient was a thin, chronically ill, white male. Bright red sputum was expectorated during examination. There was moderate dyspnea present. Blood pressure was 148/86, pulse 84, irregular with pulse deficit of 20. The chest was emphysematous. Diminished breath sounds at right base posteriorly and moist râles present at both bases. The heart was enlarged both to right and left. There was a Grade II systolic and diastolic murmur at the apex. Liver edge 4 cm. below costal margin.

Laboratory. Serology was negative. Erythrocytes and hemoglobin were within normal limits. White count was 10,600 with 92 per cent neutrophiles. Urinalysis was negative except for one plus albumen and rare hyalin casts. Roentgenogram of chest demonstrated cardiac enlargement, pulmonary emphysema and a shadow in the right lower lung fields interpreted as pulmonary edema with effusion. EKG showed auricular fibrillation and digitalis effect.

Course. The patient improved on bed rest and general supportive measures. The amount of hemoptysis progressively decreased until 2 week after admission when a sudden episode of chest pain occurred accompanied by hemoptysis. Roentgenographic examination demonstrated no change. A week later a third episode occurred. Repeated examination of the legs revealed no evidence of thrombophlebitis.

On Dec. 16, 1949, a right auricular appendectomy was performed. Pathologic report: "auricular appendage showing small organizing mural thrombus and extensive myocardial degeneration and necrobiosis." The course following operation was satisfactory. The patient was ambulatory by the sixth day after operation but required occasional nasal oxygen for 12 days for dyspnea. Accumulation of left pleural fluid required thoracentesis on 2 occasions. On January 11, 1950, a bilateral superficial femoral vein ligation was performed under local anesthesia because of mild tenderness in the right calf muscles. No evidence of thrombus formation was apparent. The patient has been transferred to the Domiciliary, where he is taking a low salt diet and 0.1 mg. of digitoxin daily. He requires 1 cc. of mercuhydrin once or twice a week. He has remained free of chest pain or hemoptysis since operation.

Case 3.—H. B., a 53-year-old retired elevator operator, was admitted January 10, 1950, complaining of pain and numbness of the right hand and forearm of 4 hours' duration. The pain was sudden in onset and was followed by numbness associated with pallor of the right hand and forearm. The pain subsided gradually and the pallor and numbness regressed. Upon admission, pain and color changes had disappeared and there was only residual weakness and coolness of the hand remaining.

Past History. At the age of 23, the patient had rheumatic fever and was treated by bed rest for 8 months. The patient was not aware of cardiac involvement. In 1947 he developed sudden severe pain in the left leg associated with numbness and coldness. He was hospitalized elsewhere and treated with anticoagulants. On that hospitalization,

he was found to have auricular fibrillation and roentgen rays showed cardiac enlargement with "right heart strain." He was placed on digitalis at that time and has been maintained on digitalis since. A similar episode of left leg pain occurred in 1948 and this was followed by intermittent claudication. In April, 1949, the patient had a pulmonary embolus and was hospitalized here. On this admission a left lumbar sympathectomy was performed for arterial insufficiency of the left leg with improvement in symptoms. He suffered a transient episode of pain in the right leg in October, 1949, and had mild intermittent claudication following this. A few weeks later a sudden attack of RLQ pain of 6 hours duration was associated with nausea and vomiting. This subsided spontaneously. He has noted occasional dyspnea and ankle edema since 1936. Past history was not remarkable otherwise except for hemorrhoidectomy in 1927, appendectomy in 1931 and herniorrhaphy in 1938.

Physical Examination. This patient was a thin white male appearing somewhat older than his stated age. Blood pressure was 120/70. Chest was clear to percussion and auscultation. His heart was enlarged 2 cm. beyond MCL, fibrillating at rate of approximately 80 with pulse deficit of 8-10. No murmurs were detected. Peripheral vessels were sclerotic and dorsalis pedis pulse absent bilaterally. Popliteal pulse was strong on the right, absent on left. The right hand was dusky and cooler than the left, but the radial and ulnar pulses were palpable and equal bilaterally. The left leg was warmer than the right. Reflexes in both upper and lower extremities were physiologic.

Laboratory. A roentgenogram of chest showed cardiac enlargement with chronic pulmonary congestion and pulmonary emphysema. Urinalysis was negative. Blood count was normal except for leukocytosis of 11,000. Kahn was positive 8 units; Wassermann negative. EKG demonstrated ventricular rate of 60 with occasional extra-systoles.

Course. Following admission the patient was given intravenous heparin for 48 hours. The hand improved progressively and appeared entirely normal by this time. Cardiac consultation was obtained, and it was decided that the patient was a suitable candidate for left auricular appendectomy. Operation was performed January 17, 1950, under endotracheal ether anesthesia. A thrombus was demonstrated in the auricular appendage at operation. Postoperatively the patient developed a tachycardia of 140 for 24 hours. He was maintained on digitoxin and the apical pulse was maintained at 90 after the first day following operation. Postoperative EKG, January 19, showed no essential change from that taken prior to surgery. Six days after operation 550 cc. of serosanguineous fluid was removed from the left pleural cavity. Seven days after operation the patient developed mild numbness and coolness of the right foot with diminution of the popliteal pulse. A right paravertebral block relieved the symptoms and improved the pulsation. Thoracentesis was again performed on the thirteenth postoperative day, 250 cc. of straw-colored fluid being withdrawn. The patient was asymptomatic thereafter and was transferred to the Domiciliary on February 14, where he receives a low salt diet and digitalis.

PREOPERATIVE PREPARATION

Patients with chronic rheumatic heart disease and auricular fibrillation with history of embolism are considered candidates for this operative procedure. It is important that a careful evaluation of the cardiac status be made under the supervision of a cardiologist. Cardiac compensation must be achneved prior to operation in these patients, who are relatively poor operative risks. Whether or not an attempt should be made to convert the fibrillation to normal sinus rhythm must be decided by the cardiologist in each individual

case. The attempt was made unsuccessfully in one of our cases (R. B.). The second patient had been found to be sensitive to quinidine on an earlier admission. The first two patients were admitted with signs of mild cardiac decompensation and were treated with a low salt diet, digitoxin and mercuhydrin. In the first case a rapid rate of fibrillation persisted. The lower extremities had undergone gangrenous changes due to arterial insufficiencies following bilateral emboli, and it was not until refrigeration to the lower thigh was instituted that the tachycardia diminished.

The selection of patients requires individual consideration of each case. At the present time, the decision for operative intervention is made by consultation between the cardiac and surgical services. It will require further experience with the procedure and a longer follow-up study of those who have been subjected to this operation before definite criteria can be established.

ANESTHESIA

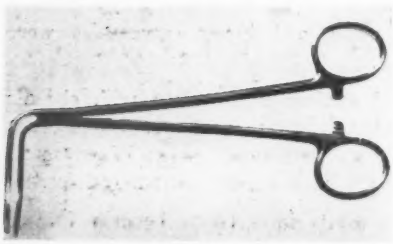


FIG. 1.—Modified right angle clamp used in resection of auricular appendage. Clamp devised from kidney pedicle clamp by removing serrations from jaws.

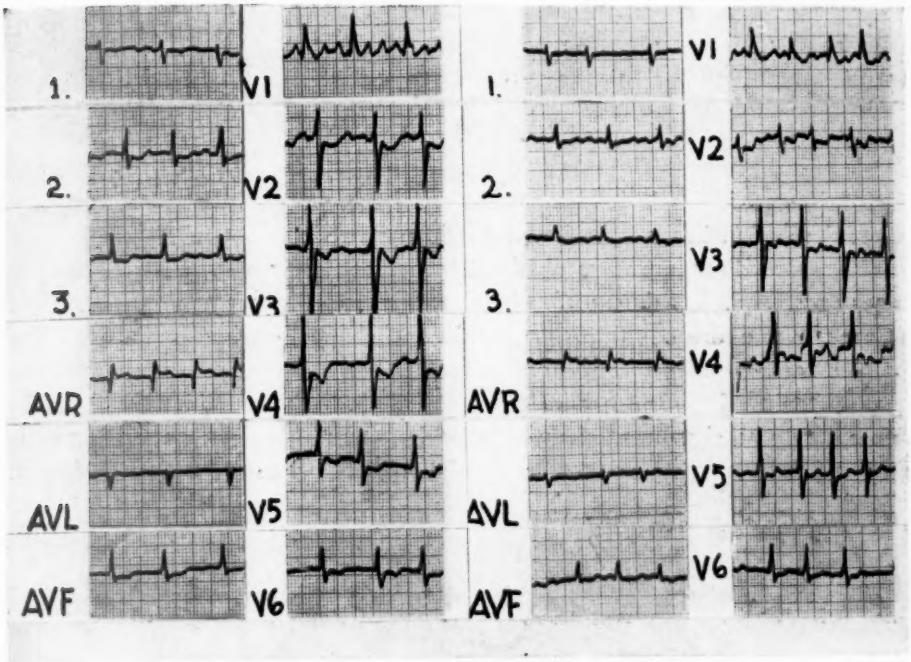
Preoperative medication and anesthesia must be selected in consultation with a competent anesthetist. In the cases reported here, morphine sulfate and atropine sulfate were administered preoperatively. Narcotics have been kept at a minimum to prevent respiratory depression. Endotracheal ether following induction with intravenous sodium pentothal has been satisfactory in this series. A high concentration of oxygen during operation is desirable.

OPERATIVE PROCEDURE

The chest is opened through the third interspace. The costal cartilage of the adjacent rib, either above or below the interspace, is divided and the ribs retracted. This provides good exposure to the left auricle, but it was found to be less satisfactory on the right side where the right auricle was found to lie in close proximity to the posterior aspect of the sternum. In this instance, it was necessary to remove a small portion of the sternum at this point. The lung is retracted gently laterally beneath a well padded broad retractor. The pericardial sac is opened in its longitudinal plane with an incision anterior to and parallel to the phrenic nerve. It has been necessary to make a perpendicular extension in the mid-portion of the pericardial incision to gain adequate access to the base of the auricle. The auricular appendage is manipulated gently during the application of the clamp to avoid accidental loosening of mural thrombi. A modified right angle, non-crushing clamp (Fig. 1) is placed across the base of the appendage and gradually closed. It is now helpful to place a smooth clamp, *e.g.*, sponge forceps, on the apex of the appendage. A

continuous suture of #00000 silk with an atraumatic needle is now placed across the base of the appendage distal to the clamp and tied at either end. The auricular appendage is now incised distal to this first suture line for a distance of approximately three-fourths its width. While the appendage is still attached, a second continuous suture of silk is placed over the end of the auricle and completed with the removal of the attached auricle. The clamp across the base is now cautiously loosened and the suture line observed for

FIG. 2



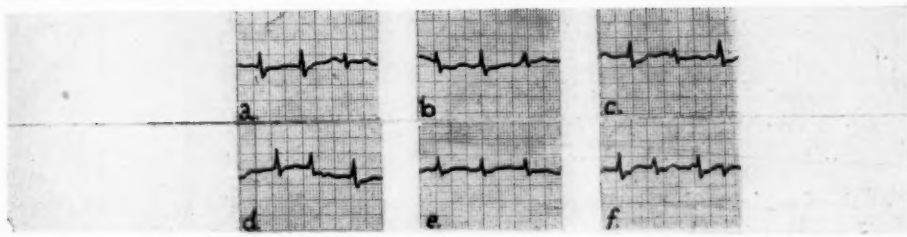


FIG. 3

FIG. 2.—Electrocardiogram from Case I (R. B.), demonstrating auricular fibrillation and right axis deviation. The tracings on the left were obtained August 8, 1949, prior to operation. The record to the right was made October 3, approximately two months after operation.

FIG. 3.—Single lead electrocardiographic records obtained during operative procedure in Case I (R. B.), August 9, 1949; (a) 8:45 A.M. following induction of anesthesia; (b) 9:00 A.M. pericardium entered; (c) 9:30 A.M. following application of clamp to base of atrial appendage; (d) 9:40 A.M. auricular appendectomy completed; (e) 10:00 A.M. pericardium closed; and (f) 10:20 A.M. operative procedure completed.

bleeding. It is usually necessary to place a few mattress sutures to obtain adequate hemostasis although bleeding has not been a problem in this series.

The pericardium is now closed with interrupted silk sutures, a defect being left in the lower end to prevent tamponade should pericardial effusion develop. The lung is allowed to expand and the chest wall closed in layers of silk. The pleural cavity is aspirated carefully and has been closed without drainage.

POSTOPERATIVE COURSE

The postoperative courses of the patients in this series have been quite satisfactory. Upon completion of the operative procedure, the tracheobronchial tree received careful attention by the anesthetist. The patient was then returned to the ward and oxygen was administered by nasal catheter. It has been necessary to administer oxygen for three to eight days after operation. Oral fluids have been given as soon as possible and the patients maintained on digitoxin and low salt intake. Ambulation has been undertaken gradually. Pleural effusion has required removal in each case.

Electrocardiograms were obtained before and after operation in the three cases presented. Tracings were obtained during operation in the first patient (Case 1) and demonstrated no significant change during operation. The pulse became regular according to palpation but the electrocardiogram shows a persistence of auricular fibrillation (Fig. 3). The postoperative tracings demonstrate no significant changes following the removal of the atrial appendage when compared with records obtained prior to operation (Figs. 2, 4 and 5).

FOLLOW-UP

The first patient (R. B.) subjected to auricular appendectomy required bilateral mid-thigh amputation for gangrene of the lower extremities. He withstood this procedure well but delayed healing of the right amputation stump prolonged hospitalization. He has had two minor episodes of cardiac failure relieved by aminophyllin and mercuhydrin. During the eight months since resection of the auricular appendage, there has been no evidence of embolus. The second case (W. D.) is now asymptomatic and is maintained in cardiac compensation on limited activity, low salt intake and mercuhydrin. The third patient (H. B.) is at present being observed for the persistent symptoms of arterial insufficiency of the right lower extremity which had been present prior to the removal of the left atrial appendage. The latter two patients have had no episodes suggesting embolism four and three months since operation, respectively.

DISCUSSION

It would now appear that removal of the auricular appendage can be accomplished in the human being with reasonable safety. It is realized that

FIG. 4

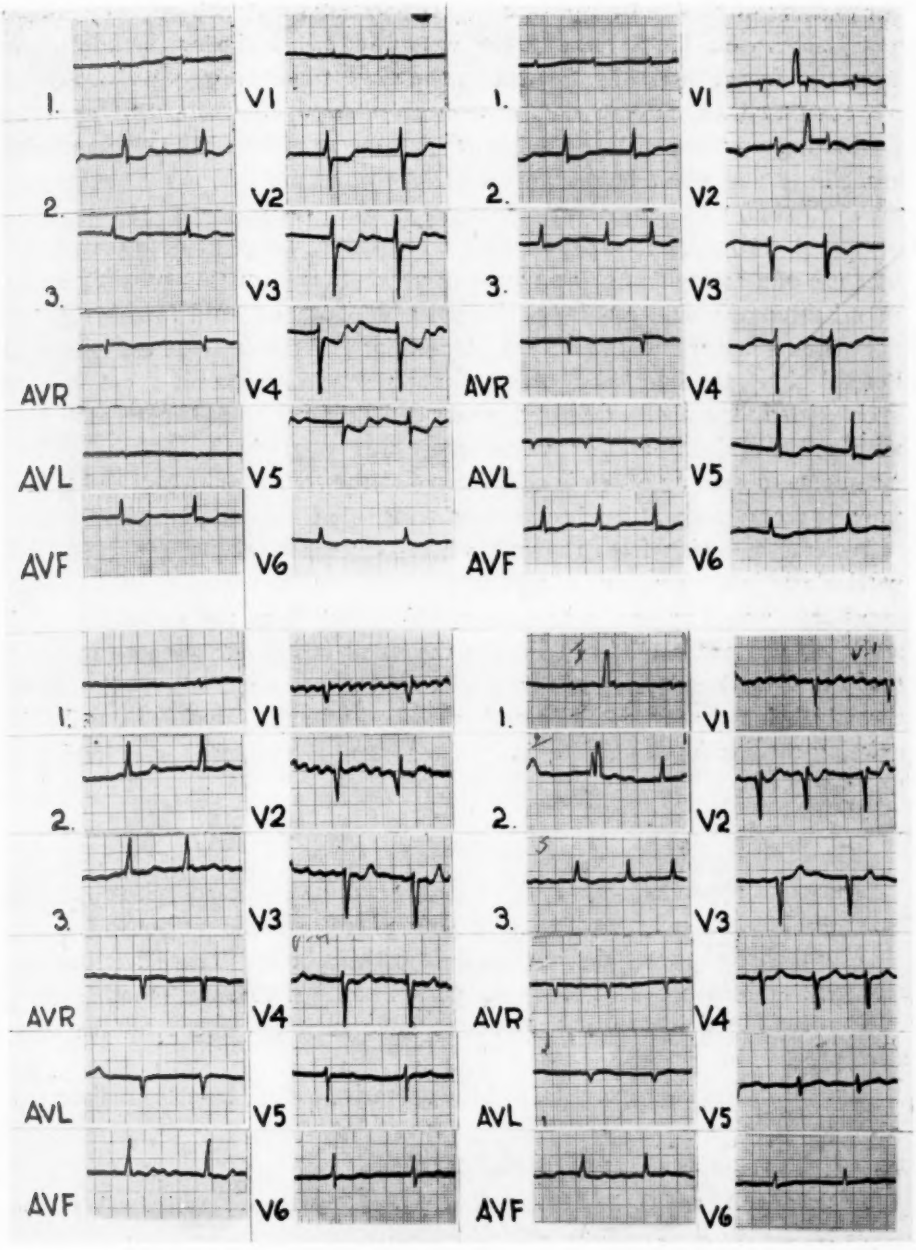


FIG. 5

FIG. 4.—Electrocardiograms from Case 2 (W. D.). The tracings to the left were obtained November 21, 1949, before operation, and those presented on the right February 3, 1950, seven weeks after operation.

FIG. 5.—Electrocardiograms from Case 3 (H. B.). The records on the left were made January 11, 1950, six days before operation, and the tracings on the right were obtained February 3, two weeks following resection of the left atrial appendage. In addition to auricular fibrillation, occasional ventricular extrasystoles are noted.

the follow-up studies are brief in the cases presented, but the results are thus far encouraging. The first patient (R. B.) in this series had multiple embolic phenomena within a period of a few weeks and has had a notable absence of such occurrence since the auricular appendage was removed.

Patients with chronic rheumatic heart disease and persistent auricular fibrillation are in constant danger of peripheral emboli with the resulting disabilities and often fatal consequences. Conversion to permanent normal sinus rhythm, which apparently does not in itself predispose to the discharge of mural thrombi, is rarely possible in cases of long-standing fibrillation. The use of anticoagulants as a means of preventing formation or discharge of mural thrombi would require prolonged administration, and these drugs are not without hazard in themselves. Heretofore, if attempts at conversion to normal sinus rhythm failed, the patients received treatment for failure, if such existed. If embolus occurred, either embolectomy or conservative therapy with anticoagulants and/or vasodilators was offered. This is essentially symptomatic therapy which is not directed at the source of emboli and fails to prevent recurrence. It has been demonstrated that the majority of the emboli in patients suffering from rheumatic heart disease originate in the auricles, particularly in the presence of auricular fibrillation. Removal of the auricular appendage would appear to be a reasonable attack upon the source of emboli and thus warrant a clinical trial. In the small group of patients presented, the procedure has been performed without operative mortality, with mural thrombi being demonstrated in each case and without interference with the existing cardiac function. The lack of recurrent embolism is encouraging in this series.

SUMMARY

Auricular appendectomy has been performed in three cases with rheumatic heart disease, auricular fibrillation and peripheral embolic phenomena.

Mural thrombi were demonstrated in each instance. There has been no recurrent embolism over a follow-up period of three to eight months.

Cardiac function does not appear to have been influenced by the operative procedures.

The indications for operation and the operative technic have been discussed.

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DISCUSSION.—DR. JOHN H. OLWIN: I should like to congratulate Drs. Longmire and Beal on the successful accomplishment of a difficult piece of surgery.

All too frequently, however, these patients are poor surgical risks, and as an alternative to surgery, I should like to present our limited experience with the use of anticoagulants in this condition.

We have given heparin and Dicumarol to six patients with auricular fibrillation and clinical evidence of peripheral emboli. In each patient the emboli apparently ceased after proper anticoagulant control was achieved.

In two instances the patients died of cerebral accidents, sudden in onset, several weeks after anticoagulants were discontinued.

A third patient remained on Dicumarol for nine months, and died three months after the withdrawal of the anticoagulant. At autopsy there was a recent coronary occlusion, with extensive myocardium infarct on, and ancient infarcts of the brain, spleen and kidneys. The latter were considered to be on the basis of old emboli. There was no evidence of recent embolism.

A fourth patient had a recurrence of his emboli ten days after anticoagulants were stopped. He was again free from them after reinstitution of the therapy, and has remained so for the past 18 months. He carries on as a laborer, and returns to the laboratory twice to three times each month for checks on his prothrombin level.

A fifth patient has been on therapy for six months, and has been free from evidence of emboli.

The sixth patient has been lost, and his present status is unknown.

In no instance was there observable evidence of emboli while the patients were on controlled anticoagulant therapy. It has been our experience that with proper methods for controlling Dicumarol administration, patients can be maintained on an out-patient basis over a period of years with safety. We have patients now who have been on as long as three and four years, with no evidence of Dicumarol poisoning being found.

It will obviously require much more extensive experience with this form of therapy before proper evaluation of it will be possible, but in patients with auricular fibrillation and recurrent emboli, who may not readily withstand surgery, this type of therapy is suggested as an alternative to surgery.

DR. IVAN D. BARONOFSKY: Dr. Longmire and Dr. Beal are to be congratulated on their excellent results. It occurred to us, at the time that Madden presented his results with auricular appendectomy, that perhaps a simpler expedient to the problem of prevention of recurrent embolization would be merely to ligate the left auricular appendage at its junction with the left atrium. In preliminary experiments in dogs, Dr. Abbott Skinner and myself found the auricular appendage actually fibrosing down to almost its disappearance in a matter of three months following the placement of a simple ligature at its base.

[Slide] With this background, we have now ligated the auricular appendage of three patients on the University of Minnesota Surgical Service at the Ancker Hospital, St. Paul. Each of these patients were rheumatics with fibrillation and evidence of embolization. In our first patient, a 47-year-old white female, a successful femoral embolectomy was performed three weeks prior to appendage ligation. She underwent a completely uneventful convalescence and has been seen six months following surgery with no complaints.

Our second patient, a 40-year-old male with auricular fibrillation, had an episode which suggested an embolus to the cerebral area with some weakness on the right side in 1943. He had a similar episode again in 1949. Ligation of the left auricular appendage was performed four months ago with a completely uneventful convalescence.

Our last patient provided us with some interesting studies. This 56-year-old rheumatic was being investigated for a rather severe melena and anemia. While a barium study was being made, she suddenly threw a femoral embolus to her right side. This was successfully removed. During her convalescence she developed signs and symptoms of a cerebral embolus. After this episode she convalesced nicely until she threw an embolus into her left femoral artery. This was removed successfully also. Two weeks after this embolectomy, auricular appendage ligation was performed with a completely uneventful convalescence. Repeated gastro-intestinal, small bowel and large bowel studies during her convalescence revealed no clue to her melena and anemia. Her anemia was controlled while on the surgical service with a transfusion every other day.

She was transferred to the division of internal medicine four weeks following surgery, for further blood studies and diagnostic procedures. At the time of her transfer she was up and about, with all wounds completely healed. Unfortunately, while on the medical service not enough vigorous treatment of the anemia was given. Three weeks after transfer to the medical service, she expired.

A postmortem was obtained and the following pertinent findings were present: No cause for the anemia could be found. [Slide] The heart showed evidence of rheumatic heart disease. There was a marked thickening of the mitral valves.

This shows the position of the umbilical tape about the base of the auricular appendage. From within [slide] a tiny ostium remains, about 3 mm. in size. In other words this tie could have been pulled just a bit tighter. The thrombus within the appendage is barely visible. [Slide] This shows a microscopic cross section of the appendage. Note the reaction around the tie. In all probability this would have constricted the ostium closed. We believe that in the future, it would be much better to place a tie of umbilical tape around the base of the auricle, and then to open the tip to remove any thrombus present. A second tie would then be used to close the opening.

[Slide] This shows a section of the brain. Note the old infarcted area. This has been present for at least a month. It probably is the evidence for the brain infarction that occurred following the first embolectomy.

[Slide] This shows evidence of old pulmonary artery embolization.

In our opinion, not only should the left appendage be ligated, but also the right, if evidence of pulmonary infarction is present. It is well known, when thrombi are present in the right side of the heart, they are usually present in the auricular appendage.

DR. ROBERT P. GLOVER: I consider it a very great privilege to be afforded this unexpected opportunity to discuss Dr. Longmire's and Dr. Beal's excellent presentation before this society. I should like to congratulate those gentlemen on their very brilliant piece of work, and to lend support to their observations and results.

Our experience with the problem of arterial embolism (and I refer also to that of my associates, Dr. Bailey and Dr. O'Neill) has been obtained indirectly during the course of our surgical efforts for the relief of mitral stenosis.

We have used the left auricular appendage as an approach to the mitral valve in 50 cases to date. In 41 of these cases the definitive operation of commissurotomy was

performed. Approximately one-half of the patients in this series presented auricular fibrillation at the time of surgical intervention. Of these, eight cases had a previous history of arterial embolism on at least two occasions. These embolic insults had resulted in disabilities ranging from complete hemiplegia to more limited peripheral paralysis.

Upon the completion of the mitral surgery, the appendages in each instance were ligated at the base, and the amputated tip oversewn. In at least four of these eight cases, the amputated tip showed the presence of partially organized thrombi.

Although these patients have continued to fibrillate to the present time, no further embolization has occurred, and no anticoagulants have been used. The follow-up period for this group ranges from two years to our most recent case, just two weeks ago. There have been no deaths in these eight cases.

We consider the superimposed presence of embolic phenomena as an urgent indication for obliteration of the appendages in mitral disease.

[Slide] At the present time our technic is to vertically incise the pericardium as you see there, either anterior or posterior to the phrenic nerve, when you will immediately see the greatly distended auricular appendage protruding. We then raise a wheal with 1 per cent procaine around the base of the appendage.

[Slide] A purse-string suture is placed around the base of the appendage. A temporary clamp is applied, [slide] and the tip amputated. The finger with the knife is inserted into the cavity of the auricle as the purse-string suture is drawn taut about the finger.

[Slide] At the conclusion of the procedure, the purse-string suture is drawn tautly, and the tip is oversewn to obtain obliteration.

Now, lest one be tempted to deviate from the technic which Dr. Longmire and Dr. Beal have discussed, or the one that you have just seen, let me give you briefly a few of the problems which presented themselves in the course of this work. Two of our early deaths resulted directly from the mismanagement of the auricular appendage. Originally, we merely inserted the finger through an incision in the tip of the appendage, and oversewed the defect when the finger was withdrawn.

One patient, well under way to recovery, died suddenly on the seventh postoperative day from a brain embolus. At postmortem examination, the thrombotic site of the appendage was found, and the embolus in the cerebellum was located.

Our technic changed immediately in the next case to include purse-stringing of the base of the appendage, but the cut tip was not sutured. We should not have relied on this mass ligature, for in the ensuing 24 hours, intermittent leakage occurred, and death followed from hemorrhage.

Since that time both methods of hemostasis have been routinely employed, and such disasters have been avoided.

Should gentle palpation of the intact appendage suggest the presence of a very large clot—as it did in another case—the purse-string suture is loosely placed at the base, the tip is amputated, and a gush of blood is permitted to wash out any loosely attached thrombotic material which might otherwise be dislodged into the circulation.

A fourth case observed on the Bellevue service of Dr. Frank Berry showed complete obliteration of the appendage by an old, completely organized thrombus. Tunneling through the fibrotic mass by sharp dissection, an opening was made of sufficient size to proceed to the mitral valve. This case was operated upon successfully by Drs. Wiley and Himmelstein.

Thus, while amputation and ligation of the appendage is essentially a safe and simple procedure, pathologic variations may occasionally present formidable difficulties.

DR. WILLIAM P. LONGMIRE, JR. (in closing): I am certain we are all agreed that the treatment of recurrent emboli in patients with rheumatic heart disease has been unsatisfactory. There are two methods which may be used in the future. One has been

suggested here by Dr. Olwin—Dicumarol therapy. The other is the surgical removal of the auricular appendage, the usual source of the emboli in this type of heart disease. Further experience with both methods will be necessary to correctly evaluate their usefulness. The difficulties of long continued administration of Dicumarol, of course, are well known. On the other hand some of these patients are very poor candidates for major surgical procedures. The first patient operated on in this series had bilateral gangrene of his lower extremities. The legs were packed in ice at the time of the auricular appendectomy.

We have felt that excision and suture of the auricular appendage creates a smoother surface on the interior of the auricle, and provides a less favorable site for subsequent thrombus formation than does a ligature or a purse-string suture about the base of the appendage.

As far as we are able to determine, the second case in this series is the only one in which a right auricular appendectomy has been performed. This patient had a series of about five pulmonary emboli prior to operation. At the time of the resection the right appendage was small and contained a small amount of thrombus.

Although there were no signs of thrombosis in the veins of the lower extremities, a bilateral femoral vein exploration was subsequently performed to rule out embolus formation in this area. These veins were found to be entirely normal. The patient has had no further pulmonary emboli during the five months since the auricular appendectomy.

BOOK REVIEW

PEDIATRIC ANESTHESIA. M. Digby Leigh, M.D., and M. Kathleen Belton, M.D.; Director of Anesthesia, Vancouver General Hospital; 240 pages; 84 illustrations; New York; The MacMillan Company; 1949.

In this volume Leigh and Belton have made one of the better contributions to the specialty of Anesthesiology. Not many anesthetists have had the opportunity to observe the disturbing effects of the various anesthetics on the physiology of large numbers of infants and children. The chief value of this volume lies in the careful observation and the suggestions the authors have made for the conduction of anesthesia based on their personal experience.

The book is divided into sections on physiology, technic, choice of anesthesia, pre- and post-operative care and specialized types of therapy. The significant statement is made that open-drop ether is still the method of choice for the untrained anesthetist. To employ the more complex technics, a long period of training and experience are necessary; but there results safer anesthesia for the child and better operating conditions for the surgeon. It will probably surprise many readers to learn that anesthesia with local agents, including subarachnoid block, comprises 12 per cent, and endotracheal technics 50 per cent of the total anesthesias administered to children. Some of the obervations made and technics employed may not prove to be entirely acceptable in the long run. However, this type of information serves more as a provocation for further investigation and as an indication of the direction in which further progress is to be made.

This is not merely a book for the anesthesiologist. It is highly recommended for perusal by the surgeon and the pediatrician. There is enough new information in this book so that all may profit by reading it.

L. D. VANDAM, M.D.

GENERAL HYPOTHERMIA FOR EXPERIMENTAL INTRACARDIAC SURGERY*

THE USE OF ELECTROPHRENIC RESPIRATIONS, AN ARTIFICIAL PACEMAKER FOR CARDIAC STANDSTILL, AND RADIO-FREQUENCY REWARMING IN GENERAL HYPOTHERMIA

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General hypothermia is being investigated as a means of reducing the oxygen requirements of the body sufficiently to allow exclusion of the heart from the circulation, thereby permitting intracardiac surgery under direct vision.

During the last two years, an interdepartmental research team has studied oxygen transport and utilization in dogs at low body temperatures[1] and has investigated the factors governing survival in hypothermia.[2] A total of 176 dogs have been cooled. Continued improvement in our technic of cooling and re-warming has made reduction of body temperature to 20°C in dogs a relatively safe procedure. However the minimal temperature with survival has been 15°C. There are no ill effects from cooling to 20°C. Death at lower temperatures is usually due to ventricular fibrillation. Below 28°C the animal enters a state of "cold narcosis" in which an anesthetic agent is no longer necessary to maintain unconsciousness and relaxation. At 20°C the oxygen consumption, cardiac output, blood pressure and heart rate are about 15 per cent of normal. With the knowledge that hibernating mammals of similar normal anatomy can survive body temperature of 3°C,[3] we have been encouraged to seek a method of reducing temperatures in dogs below the present critical level.

COOLING WITH "ELECTROPHRENIC RESPIRATION"

The present method of cooling, using two blankets containing coils with circulating refrigerant** has already been described.[1, 2] The animals are given digoxin and procaine intravenously initially and hypothermia is then induced with the aid of intravenous pentothal and curare to control shivering. About half of the animals have been heparinized with no recognizable effects on the

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cooling pattern. Venesection is used for abnormal increase in venous pressure. Continuous cathode-ray electrocardiograph visualization is used.*

Recently artificial respiration, necessary at lower body temperature, has been carried out by the periodic stimulation of the exposed phrenic nerve, as described recently[4] as the "electrophrenic respiration." A stimulator† with a rotating potentiometer‡ has been used as an electrical source. This device delivers any type of electrical current in periodic bursts of desired duration or frequency. The respiratory rate is varied simply by adjusting a dial.

This technic has been used 30 times. Continuous venous pressures from the superior vena cava have been observed in each experiment. Electrophrenic respirations applied in the presence of a positive venous pressure have invariably caused a reduction, and pressures below zero cm. of water have been maintained in nearly all animals.

One phrenic nerve only is stimulated. Optimum results are obtained when the stimulating electrode is in contact with all roots of the nerve, at which time an excellent respiratory excursion is obtained which easily maintains full arterial oxygen saturation. In the dog which has normally a communication between pleural cavities these diaphragmatic movements are of no value with the chest open. At such times positive pressure respirations are instituted.

EXCLUSION OF THE HEART AND CARDIOTOMY

It has been possible at a body temperature of 20°C to exclude the heart from the circulation for periods of 15 minutes with survival. In some of the animals during the period of exclusion the heart has been opened and then sutured.

Although further physiologic studies are in progress and methods of cooling are being investigated which may allow reduction of the body temperature with safety to below 20°C, it was decided to test our hypothesis by operating at this temperature. Using sterile technic the fifth rib is removed and the chest opened. Bull dog clamps are applied to the superior and inferior venae cavae and azygos vein. This prevents all blood from entering the heart except that from the mouth of the coronary sinus, which is reduced to a slow ooze because of the low arterial pressure.

No attempt has been made to carry out intracardiac procedures or investigate special exposures. The cardiotomy performed is a token operation. Once the heart is excluded from the circulation, the pericardium is incised and after surface application of cocaine the right auricle is opened with exploration of right auricle and ventricle. Several technics have been used to attempt to eliminate or minimize air embolism. Usually during closure of the cardiac muscle the chambers are filled with heparin-saline solution. With

* Smith and Stone, Ltd., Georgetown, Ontario.
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‡ National Research Council, Ottawa, Canada.

completion of the cardiotomy the clamps are removed and the chest closed. Re-warming is commenced immediately.

When the clamps are applied, the heart appears empty and the auricle no longer fills in diastole. Its rate, reduced by hypothermia to 20 per minute, usually increases four or five beats per minute. Incision into the auricle is well tolerated and has never precipitated ventricular fibrillation.

In 39 dogs the heart has been excluded from the circulation in the manner described for periods of 15 minutes or more at a body temperature of 20°C. On 23 of these a cardiotomy was performed. Nineteen, or 49 per cent of the

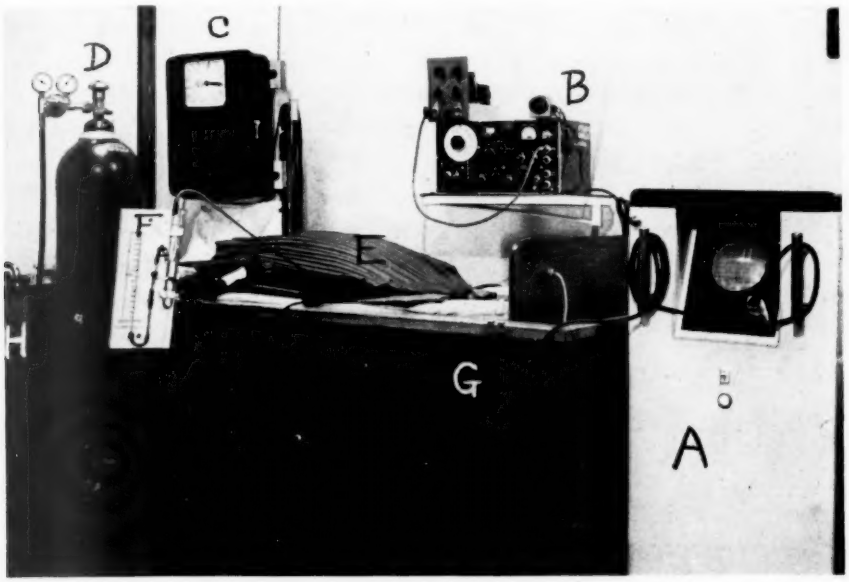

FIG. 1

A. Continuous cathode-ray electrocardiograph.
B. Electric stimulator.
C. Thermometer.
D. Oxygen tank.
E. Animal wrapped in cooling blankets containing coils of circulating refrigerant at 0°C.
F. Venous pressure and blood pressure Manometers.
G. Diathermy re-warming cabinet (lower half).
H. Refrigerating machine.

total, died either during the clamp-off period or during re-warming. Twenty, or 51 per cent of the total (including 11 with cardiotomy) were revived to normal body temperature.

Of those dying in the cold state, five experienced cardiac standstill, while the remaining 14 died from ventricular fibrillation. Six deaths occurred during the clamp-off period, six immediately after removing the clamps and seven during re-warming. Some of the deaths immediately after removal of the clamps may have been caused by removing the clamps too rapidly, with

overfilling of the heart. Most of the deaths in the re-warming period occurred around 32°C.

Of the 20 animals revived to normal body temperature and returned to their cages, six survived the procedure completely. Of these, two were sacrificed during the second week because of gross wound infection and the remaining four were used several weeks later for other cooling experiments. After an initial period of lethargy and weakness, these animals resumed apparently normal activity within a few days.

The remaining 12 with good respiratory function and normal electrocardiograph tracings at normal body temperature developed a state of shock which appeared in two to 12 hours. This was characterized by a progressive fall in blood pressure with cyanosis. Observations of blood pressure and venous pressure, together with blood oxygen and hematocrit studies and routine postmortem examinations, have not as yet given us a full understanding of this shock state.

As a rough index of their tolerance to severe cold two dogs were cooled to 20°C and were maintained at this temperature until death from ventricular fibrillation. They lived 17 and 20 hours with a persistently good electrocardiographic tracing. Their total periods of hypothermia were 27 and 28 hours.

DEFIBRILLATION

Our early attempts at defibrillation have been reported.[2] In the present series this has been attempted in ten experiments and has been successful six times. In five of these cases spontaneous heart beat returned, but the sixth remained in cardiac standstill. Those hearts with a weak ventricular fibrillation did not respond, or responded poorly to defibrillation.

The defibrillating shock is delivered to the heart through nickel-plated electrodes mounted upon an insulated handle after the method of Hooker, *et al.*,[5] Beck and Mautz,[6] using 50 to 120 volts, and frequencies of 25 to 60 cycles per second.

AN ARTIFICIAL PACEMAKER FOR CARDIAC STANDSTILL

Medical men have little fear of temporary cessation of respiration and successfully apply artificial respiration in several forms for prolonged periods. With evidence that many hearts, including those in the hypothermic state, which have ceased beating still have the power to contract following mechanical stimulation,[7] it seemed reasonable to consider the use of an artificial pacemaker to restore heart function. It was felt that, using the principle of electrophrenic respiration, periodic electrical stimulation of S-A nodal area might restore the beat. This could conceivably be carried out for prolonged periods until the organism had been restored to a state where spontaneous normal heart action was regained. As yet no report of a similar technic used in the intact animal has been found in the literature.

This is a very early report of such a procedure which has been attempted recently in four cases of cardiac standstill, in each case with restoration of heart action. The stimulator, with rotating potentiometer, has been used to deliver impulses at any desired rate. An indifferent electrode is clipped onto the chest wall and the stimulating electrode placed in the region of the S-A node. Normal appearing heart action is observed and the heart rate is varied within limits by adjusting a dial.

In two experiments the artificial pacemaker was used for ten to 15 minutes, and when it was discontinued the heart returned to standstill. In the other two animals following electrical control of the heart beat for ten and 30 minutes, normal spontaneous heart beats returned.

In one of these following cardiotomy at 20°C the heart was sutured and clamps removed. Ten minutes later in the presence of good vigorous heart action and normal venous pressure, ventricular fibrillation set in. The heart was defibrillated by the technic described, producing cardiac standstill. Electrical stimulation of the S-A nodal area was then carried out for ten minutes, testing effect of withdrawal of this at intervals until spontaneous heart action was restored. The chest was closed and the dog re-warmed to normal body temperature, only to die several hours later.

Defibrillation following cardiac massage has been used to revive animals[8] and human beings,[6] and we have used cardiac massage for periods up to ten minutes, with return of normal heart action and revival. However, the possible advantages in hypothermia where the stimulating wire could be left in place during closure of chest and re-warming are obvious. Should such a technic prove worthwhile, its extension to other clinical conditions with cardiac arrest might be considered.

RADIO-FREQUENCY REWARMING

Radio-frequency re-warming has been used successfully on hypothermic animals. Until recently, re-warming has been carried out by immersion of the animal in a water bath at a temperature of 40°C. Such a technic, although successful, has the theoretical disadvantage of re-warming superficial structures before the heart and blood stream. It was considered to have several unsatisfactory features, should hypothermia ever come to be applied to surgery on human beings.

Since 1900, short wave diathermy has been used extensively to study the production of hyperthermia from normal body temperature.[9] More recently, microwave diathermy has been used in similar investigations.[10] No reference has been found to their use in deep hypothermia. In our re-warming experiments, ordinary microwave and short wave capacitive heating diathermy technics were found unsatisfactory, due either to localized or inadequate general heating, or to electrode burns. Further investigation indicated that inductive heating was a preferable technic, providing greater facility of application, reduced danger of superficial burning, and more generalized heating. In this

type of heating, eddy currents are set up in the tissue within the influence of the electro-magnetic field of the induction coils. The heating action is caused by the conversion of the eddy currents to heat within the tissues. Since the vascular tissues produce a greater concentration of eddy currents our coils were arranged so as to parallel the main blood vessels, thus enhancing heat distribution throughout the body.

No optimum frequency was found within the usual short wave diathermy range. The rate of re-warming at 27 mc and 13 mc was about the same. However, at the lower frequency, the danger of coil burns was reduced.

A shielded radio-frequency heating cabinet was constructed along the lines of a conventional hyperthemia cabinet, with supplementary air heating to minimize heat losses by conduction. With this cabinet nine animals have been re-warmed and all successfully returned from an initial 15° to 20°C to normal body temperature. The rate of re-warming has varied between 3°C and 13°C per hour as a result of variation in experimental technic. The first two, imperfectly insulated, suffered extensive superficial burns, two others had a local reaction about the metal electrocardiographic electrodes, and five were free of any apparent ill effects.

At the present time a frequency of 14 megacycles is under study with induction coil-type applicators. This method is simpler than water immersion and allows easier access to the animal. It is felt that a satisfactory and safe technic is being developed, although an assessment of possible late ill effects is not yet possible.

DISCUSSION

At normal body temperature of 38°C a dog will survive exclusion of its heart from the circulation from five to nine minutes.[11] Although the final survival rate of 15 per cent in this study following 15 minute exclusion of the heart at low body temperature is not very impressive, 85 per cent survived the actual clamp-off period. This suggests that our basic hypothesis may be correct.

With a greater knowledge of the physiology of hypothermia it may be possible to endow non-hibernating mammals with the ability to survive even lower temperatures than those tolerated thus far. Temperatures below 20°C would further reduce the tissue oxygen requirements and would conceivably increase the length of time an animal could tolerate interruption of its circulation. Should deep hypothermia be developed as a safe surgical technic, it might be expected to extend the scope of surgery in other fields.

Reference has already been made[2] to the many problems that must be solved to understand even the elementary changes in hypothermia. One is encouraged in this study, however, by our knowledge of the tolerance to cold exhibited by hibernating animals and the reports of human survival from temperatures as low as 25°C.

SUMMARY

1. It has been possible to exclude the heart from the circulation for periods of 15 minutes in dogs at a body temperature of 20°C with survival. In most of these animals during the period of exclusion the heart has been opened and then sutured. This procedure is attended by a high mortality and the cause of death is not clearly understood.

2. Periodic electrical stimulation of the phrenic nerve has been used as a form of artificial respiration during the period of respiratory depression in the lower temperature range.

3. Electrical defibrillation of the heart has been practiced.

4. An artificial pacemaker in the form of periodic electrical stimulation of the S A node area of the heart has successfully restored heart action in cardiac standstill in the cold state.

5. Radio frequency re-warming procedures have been studied.

We would like to acknowledge the valuable technical assistance of Mr. Donald Hughes.

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DISCUSSION.—DR. WILLIAM L. RIKER: We have enjoyed this paper very much, and wish to present some of the clinical applications of hypothermia. For the past two years at the Children's Memorial Hospital in Chicago, we have been interested in reducing the temperature of patients undergoing major surgical procedures, for two reasons. In the first place, we want to control hyperpyrexia. In more than a hundred

unselected major surgical procedures the temperatures were recorded, and it was found that in 60 per cent of the patients the rectal temperature went over 100 degrees. In 20 per cent of the patients the rectal temperature exceeded 102 degrees. In some patients the rectal temperature went up exceedingly high. We had two fatalities attributed to hyperpyrexia before we began the cooling procedure.

In the second place, we felt that in the cyanotic cardiac cases, hyperthermia during operation with increase in oxygen requirement, might be disastrous, while hypothermia, on the other hand, would lower the oxygen requirement and reduce our operative risks.

[Slide] This shows the apparatus that has been used. It has been simplified somewhat recently. On the right we see an oven with a constant temperature, in which one thermocouple is kept. Here is another thermocouple which is inserted in the rectum. In the operating room there is a galvanometer which allows us to read off the rectal temperature at any time during the operation.

Here we have a water mattress, which may be filled with either cold water or warm water, and can be emptied whenever we want to change the temperatures.

In applying the cooling system in the cases of non-cyanotic patients, we have attempted only to keep the rectal temperature as near normal as is possible. We have used the cooling system only in those cases in which the temperatures rose above normal. In none of the patients, since we have been using the cooling system, has the temperature gone over 102 degrees rectally, even in the hottest part of the season in Chicago.

In the cyanotic group we have attempted to keep the patient's temperature below normal, down to 96 degrees Fahrenheit if it is at all possible. In the extremely poor risks we have even lowered the rectal temperature to 93 degrees Fahrenheit.

As to results, out of 109 cases that were not cooled (before we had the system we are now using) eight patients developed signs of severe anoxia. Four of these patients died from anoxia. Since we have been cooling the patients, only three of the 128 cyanotic heart cases operated upon have shown any degree of severe anoxia. There were only two deaths attributable to anoxia. We therefore feel that in the cyanotic cardiac cases if you can produce a hypothermia during surgical procedures it gives a much smoother anesthesia, the operative course is much easier, and it decreases the evidence of severe anoxia and mortality postoperatively.

Dr. Warfield M. Firor: An interesting corollary to this whole subject is an observation and experiment that was carried out in the tissue culture laboratory of the Department of Surgery at Johns Hopkins.

Until three years ago it was thought that the maintenance of a temperature of approximately 37° C. was essential to the viability of mammalian cells in tissue culture. It was shown, however, by Gey that one can maintain a variety of mammalian tissues in a viable state for periods of six weeks at a temperature as low as 28 degrees centigrade.

Certain basic biologic phenomena can be studied under this experiment. It has been observed that cell division continues at the reduced temperature, and that the process of cell growth appears to be altered, because in many instances innumerable giant cells appeared in the cultures.

The morphology of these cells did not in any way simulate the alteration of a benign to a malignant cell, but, nevertheless, this offers one tool for understanding something of the growth process of mammalian tissue.

Dr. Clarence Dennis: With considerable misgivings, Mr. Chairman, in the presence of pioneers like Dr. Crafoord and Dr. Bjork and Dr. Gibbon, I feel this is the proper time to say a little bit about the experimental work that our group has been doing in the laboratory at Minnesota. Our group includes also Dr. R. M. Nelson, Dr. W. P. Eder and Dr. K. E. Karlson.

The primary reason for getting up to say anything seems to me to be the observations by Dr Bigelow and his associates, in their excellent study, of the death of about two-thirds of the animals who apparently had recovered at the time of return to normal temperature. This is one of our major problems as well.

With the apparatus which we are using at the present time, which consists of a modification of Gibbon's apparatus and a considerable modification of that of Crafoord and Bjork, we have found that we can carry on oxygenation satisfactory to carry an extra corporeal cardiac and pulmonary circulation for a period of half an hour in a dog of 70 pounds. We are able to pump about 2800 cc. of blood per minute, with a saturation of over 90 per cent, for periods of about one-half hour. We can introduce about 200 cc. of oxygen per minute.

We have been successful in opening the right ventricle of the heart, closing the ventricle, carrying the dog for half an hour on the machine, and having the dog recover.

The longest period we have carried our dogs is a little over an hour, but that dog did not recover.

Hemorrhage is no longer a problem. Foaming seems no longer to be a problem. Our chief problem seems to be the late death, such as Dr. Bigelow has observed.

It occurred to us that the rise in the blood sugar level, which is consistently seen during this profusion, and the drop in the blood pH which occurs in spite of the maintenance of the normal partial pressure of carbon dioxide, and good oxygenation, should suggest that there is something wrong with the intermediary metabolism of carbohydrate. We have started out by working on some of these enzymes, with the cytochromes in particular. We find that there is an increase in the concentration of pyruvic acid and of lactic acid in the blood during the course of these profusions, and, furthermore, that in some of these animals the pyruvic acid and lactic acid level can be returned, not to, but toward, normal, by the continuous infusion of cytochrome or cytochrome oxydase into the circulating blood in the machine.

Of interest, however, is the late death of these animals. Normal pyruvic acid levels run about 1 mg. per 100 cc. At the end of the profusion we are usually under 2 mg. per 100 cc. The dogs begin to recover, and begin to whine, maybe moving around, and occasionally one has been up and around, and on drawing specimens of blood for various studies at varying periods of time afterward, we have found some dogs that have gone five or six hours when some sort of poorly understood compensation breaks, and the pyruvic acid goes to very high levels. Our highest has been 8 mg. per 100 cc. That dog died shortly afterward. The mechanism of this is under study; we have no explanation for it.

Dr. W. G. Bigelow (in closing): I was very interested in what Dr. Frior said about tissue cultures. We are starting a similar study. His observations concerning cell division at 28° C. are very interesting. I do not know whether our delayed shock is the same problem that Dr. Dennis had in his extra corporeal circulation studies. We deal with other factors, such as hypothermia and an interrupted circulation, but his references to pH are interesting.

Our professor of pathologic chemistry, Dr. J. Dauphinee, and Dr. R. Fleming, have been working on a biochemical study. They have gone away past my comprehension now, but they do not seem to have come up with all the answers as yet.

These animals develop an acidosis with a pH down to 6.6. It would appear to be principally a gaseous acidosis. In the hypothermic state one is dealing with variations in solubility as well as availability of gases in the blood, together with fluid and electrolyte shifts. Thus it is a complex study.

I would like to thank the discussers and also thank the society for the privilege of presenting this paper.

SHOULD TOTAL GASTRECTOMY BE EMPLOYED IN EARLY CARCINOMA OF THE STOMACH?*

EXPERIENCE WITH 139 TOTAL GASTRECTOMIES

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TOTAL GASTRECTOMY has now been done over a sufficient number of years to make it worth while to attempt to evaluate its effectiveness and possible place in the radical treatment of gastric cancer. As has been proper up to now, practically all of the operations of total gastrectomy from which figures of five-year survival can be obtained have been done in cases in which the cancer of the stomach was too advanced to be completely removed by partial gastrectomy. In some of these cases, total gastrectomy had been employed for carcinoma of the stomach which involved the cardia or upper portion of the stomach in which, by an abdominal approach, the entire stomach with its tumor could be removed and an esophagojejunal anastomosis made. It is of interest to note in the last ten years the development of total gastrectomy as a radical method for removal of cancer of the stomach and also to note the increase in the number of total gastrectomies being done in the later years as well as the significant general decrease in the operative mortality of this operation.

Finney and Rienhoff[4] reviewed the literature on total gastrectomy in 1929 and were able to report a total of 67 patients who had been subjected to this radical operative procedure, including five cases of their own. The operative mortality was 53.4 per cent, and in 58 per cent of those cases the cause of death was peritonitis. Our interest in total gastrectomy dates from 1927 when the first total removal of the stomach was done in this clinic. In 1938, eight cases of total gastrectomy were reported from this clinic by one of us[5] (F. H. L.) with three postoperative deaths. In 1944,[7] 65 additional cases, making in all 73 cases, were reported, with an operative mortality of 33 per cent. This report was compiled in November, 1943, and did not include two cases in which total gastrectomy was done shortly after the paper was submitted for publication, making a total of 75 cases of total gastrectomy up to the end of 1943 (Table I). We have now done 139 complete gastrectomies, of which 127 were for malignant tumors of the stomach and 12 for benign gastric ulcer (Table I). From January 1, 1944, to March 1, 1950, 64 total gastrectomies have been done, with six postoperative deaths, an operative mortality of 9.4 per cent, whereas there was one death in a group of 12 total gastrectomies for

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peptic ulcer, an operative mortality of 8.3 per cent. It is apparent that a sufficient number of total gastrectomies have now been performed to demonstrate that the mortality of total gastrectomy can be brought within the same range as partial gastrectomy. It is evident from our figures for 1944 to 1950 that the operative mortality of total gastrectomy is now no higher than that of partial gastrectomy. The mortality of partial gastrectomy for malignant disease of the stomach from 1937 to July 1949 was 9.2 per cent.

Numerous articles in the recent surgical literature record decreasing mortality rates for total gastrectomy. Farris, Ransom and Coller[3] reported only two deaths in a consecutive series of 19 cases, a mortality of 10.5 per cent. Scott and Longmire,[13] in reporting on 63 cases of total gastrectomy in 1949, gave a mortality rate of 9.5 per cent. At present, however, figures on survival rates after total gastrectomy are too small and the number of cases of total gastrectomy is still not sufficiently large to make worthwhile comparison with the results obtained following partial gastric resection for carcinoma, nor could the analogy be made upon truly comparable groups of cases, since total

TABLE I.—*Total Gastrectomy—139 Cases.*

	Patients	Postoperative Deaths	Mortality, Per cent
1927–1943	75	26	34.6
1944–1950 (March 1)	64	6	9.4
	139	32	

gastrectomy has up to the present time been employed almost exclusively in the more widespread type of gastric malignancy too extensive to permit the use of partial gastrectomy.

In view of this satisfying lowered mortality rate now accompanying total gastrectomy for the treatment of late gastric cancer, one of us[6] (F. H. L.) in a recent editorial stated that the time is now at hand to consider a more aggressive surgical approach to the treatment of intermediate and early gastric malignancy with the hope that we may thus improve the five-year survival rate which, with partial gastrectomy, is now so deplorably low. As shown in Figure 1, total gastrectomy for cancer, when compared with other radical operations for cancer, does more satisfactorily fulfill the requirements of radical removal of the lesions and the adjacent nodes than does subtotal gastrectomy. Pack and McNeer[12] have recently quite properly emphasized the fact that any improvement in our results of the treatment of gastric cancer will be obtained only by increasing the resectability rate and by resecting all gastric cancers that are technically removable. This, of course, would mean not only wide extirpation of the gastric cancer itself and its lymphatic distribution but also the radical removal of any involved adjacent organs. That partial gastrectomy has resulted in a very low five-year survival rate is illustrated by the 20 per cent five-year survival rate in resected cases reported by

Welch and Allen.[16] Our own five-year survival rate is similar, 22.3 per cent of those patients who survived resection. Pack and McNeer[12] reported that 34.7 per cent of 75 patients surviving partial gastrectomy lived five years without recurrence. When one considers that approximately only one in four of those patients who come to surgery with the diagnosis of cancer of the stomach can have a resection, the survival rate for the entire group that enters the hospital is very low indeed. During the period 1936 to 1940 in this clinic only 24.1 per cent of the patients operated upon for cancer of the stomach had resection, but since that period we have gradually increased the resectability rate in these cases to 37 per cent (1940-1945).

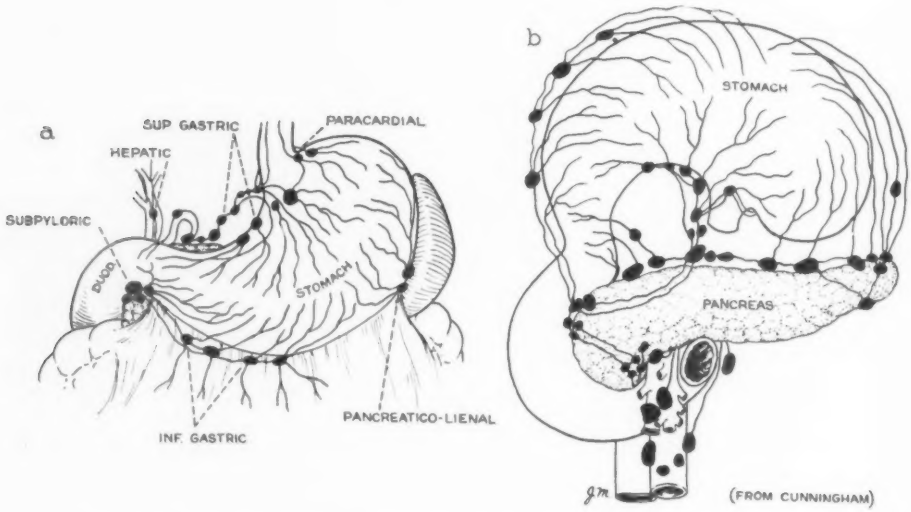


FIG. 1.—Note the node distribution of the stomach and how incomplete in terms of radicalness any operation short of total gastrectomy is for cancer of the stomach. (a) Lymph nodes over anterior surface of stomach and omentum; (b) Stomach elevated to show lymph nodes of posterior surface.

Inasmuch as total gastrectomy has been done in many cases in which the lesion involves the upper half of the stomach or the gastric cardia it is of interest to compare these results and note the operative mortality associated with the transthoracic approach to this problem. Sweet,[14] in 1948, reported 86 cases of gastric carcinoma invading the cardia and lower esophagus in which resection and primary anastomosis were done with ten deaths, a mortality of 11.6 per cent. In the same year, Pack and McNeer[11] reported 65 cardiectomies with an operative mortality of 32 per cent. In the majority of this latter group resection was done by the transthoracic approach.

In any discussion of total gastrectomy there will always arise the discussion about whether or not total gastrectomies should always be done through the chest. This question will never be completely settled. Our position on it is that when there is any question about extension beyond the diaphragm,

it should be approached transthoracically and when the esophagus can be demonstrated as free, we prefer the abdominal route. Our inclination is toward the abdominal route, because in few of the patients with carcinoma of the stomach which has extended upward along the esophagus will the tumor prove to be operable. In addition, we prefer the abdominal approach because it is easier for us to do low resections of the duodenum close to the common duct by this approach and also because in occasional cases we have had to remove the left half of the pancreas, the transverse colon or the left lobe of the liver when those structures have been involved in the growth by direct contact.

TABLE II.—*Total Gastrectomy for Malignancy—127 Cases.*

Sex		Age, years	
Males	77	20–30	2
Females	50	31–40	7
	127	41–50	29
		51–60	42
		61–70	34
		71–80	13
			127

In the light of our present knowledge the only available method of treatment for cancer of the stomach is radical surgical removal. The early diagnosis of cancer of the stomach has not appeared to improve very much over the past few years. However, if more attention could be paid to digestive complaints in patients over the age of 45, an earlier diagnosis would be possible in a much larger group of these patients. It is significant to emphasize

TABLE III.—*Duration of Symptoms (127 Cancer Cases).*

Symptoms		Patients
Less than 3 months		42
3 months or more		85
3 to 6 months	18	
6 to 9 months	31	
9 to 12 months	6	
1 year or more	30	
		127

that the annual death rate for cancer of the stomach in 1945 was 11 per 100,000 for all persons from 1 to 74 years, whereas between the ages of 45 and 74 the annual death rate for cancer of the stomach was 53.7 per 100,000.[9] It is also of considerable significance to point out that of the total deaths each year, approximately 13.5 per cent are caused by cancer in all its forms, whereas 3.1 per cent of the total number of deaths were from cancer of the stomach. Cancer of the stomach is the most common form of malignant disease. This is particularly true in males past the age of 45.

In this group of 127 patients having total gastrectomies for carcinoma, 77 were males and 50 were females (Table II), which is about the proportion

given by the United States Bureau of Vital Statistics for carcinoma of the stomach in males and females, a ratio of 20 to 12. In this group of 127 patients with gastric cancer who had had total gastrectomy, 92 per cent were above the age of 40 (Table II), the youngest being 27 years of age and the oldest 78. A discouraging feature in regard to the early diagnosis of this lesion is the duration of symptoms before a patient seeks medical aid or before the diagnosis is established. Of the group of 127 patients who had total gastrectomies done for gastric carcinomas, 42 patients had had symptoms for three months or less and 85 had had symptoms for from three months

TABLE IV.—*Delay in Treatment.*

	Patients	
Delay due to		
Physician	53	
Patient	32	85
No delay (symptoms less than 3 months)		42
Total		127

to a year or more (Table III). Thirty patients had had considerable gastric distress for a year or more. Among the patients who had symptoms for three months to a year or more the delay was the responsibility of the physician in 53 cases, either because of a lack of diagnosis or an erroneous diagnosis, and was due to the patient's failure to seek medical aid in 32 cases (Table IV). The relationship of benign gastric ulcer to the development of gastric cancer is something which has concerned every surgeon operating upon many patients with gastric cancer. Fifteen patients had a history for several years which was strongly suggestive of untreated ulcer, and 26 patients actually had been

TABLE V.—*Delay in Surgical Treatment Three Months or More From Onset of Symptoms—127 Cases.*

Cause	Patients
Ulcer history—untreated	15
Treated for ulcer	26
Primary or secondary anemia (treated)	5

treated for ulcer over long periods without roentgenologic examinations; five patients had been treated for primary or secondary anemia (Table V). There were only 42 patients in the entire group who had had symptoms for less than three months, which we think justified classification as no delay in diagnosis, as they presumably came for diagnosis and treatment within a fairly reasonable period. It is quite apparent, in the study of these cases, that the correct roentgenologic diagnosis is related to the skill and experience of the roentgenologist.

As one studies the histories of these cases, one's attention is constantly called to the necessity for greater wariness concerning all digestive disorders

in patients past the age of 45. In this group of cases (Table VI) the most common earliest symptom noted was epigastric pain or discomfort which occurred in 79 patients. The most common symptoms which were noted in all of these cases (Table VII) were pain, weight loss and anorexia, and

TABLE VI.—*Total Gastrectomy for Carcinoma—127 Cases; Earliest Symptom Noted in Individual Cases.*

Symptom First Noted	Cases
Epigastric pain or discomfort	79
Anorexia	11
Dysphagia	9
Flatulence	7
Nausea or vomiting	8
Bleeding	5
Hematemesis	
Melena	
Anemia	3
Pallor	
Weakness	
Weight loss	4
Diarrhea	1
	127

those patients who had neoplasms which were far advanced when seen by the physician complained more frequently of nausea and vomiting, malnutrition and anemia.

Even granting that total gastrectomy was done in practically all of these cases for advanced or widespread malignant disease involving the greater portion of the stomach (Table VIII), anemia was not an outstanding sign or symptom, as there were only 29 patients with a hemoglobin of less than 75 per cent and 21 patients with a red count of less than 4,000,000. Determination of the gastric acids was not particularly significant; 50 patients had no free hydrochloric acid in their gastric contents and 23 patients had less than 20. From these figures it can again be emphasized that in a patient with

TABLE VII.—*Total Gastrectomy—127 Cases of Carcinoma; Symptoms in Order of Frequency.*

Pain	99	Vomiting	21
Weight loss	98	Bleeding	11
Anorexia	54	Hematemesis	
Flatulence	31	In stool	
Nausea	22	Dysphagia	10
		Anemia	5

gastric symptoms an achlorhydria is of great significance and may well indicate gastric neoplasm, whereas the presence of free hydrochloric acid, as is well known, is no assurance of the absence of malignant disease in the stomach.

One of the most common and also variable characteristics of malignant tumors is their ability to metastasize to regional lymph nodes. The extent of such lymph node involvement is considered a quite reliable criterion on which to base the prognosis in an individual case. This has been of considerable

prognostic significance in carcinomas of the intestine and of the breast. Recently, Moore[10] and his associates have suggested that the lymph node involvement from cancer of the stomach might be of some prognostic significance in those cases, and they thought that the presence or absence of demonstrable metastases in the regional lymph nodes has great prognostic value. They reported that in 100 patients surviving resection, 29 lived three years and 13 lived five years; 71.4 per cent of those without involvement of lymph nodes lived three years or longer, whereas only 17.7 per cent with involvement lived three years or longer. In our group of 127 patients who had total gastrectomy, 83, or 65.4 per cent, had involvement of lymph nodes, and only 44, or 34.6 per cent showed no metastases to lymph nodes. It will be shown later in Table XIII that this was of some significance in the ultimate survival, as a somewhat larger group of patients survived for longer periods when there was no involvement of lymph nodes than did those with node metastases.

TABLE VIII.—*Total Gastrectomy for Carcinoma—127 Cases; Laboratory Data.*

	Cases
Gastric contents	
No free hydrochloric acid	50
Free hydrochloric acid less than 20	23
Anemia	
Hemoglobin less than 75%	29
Erythrocytes less than 4,000,000	21

TABLE IX.—*Length of Survival in Patients With Extension of Carcinoma Near or Through Line of Resection—12 Cases.*

	Cases
Postoperative death	3
Lived less than 6 months	2
Lived 6 months or more	4*
Lived 1 year	1
Lived 1½ years	1
Lived 2 years	1
Total	12

* 3 lived six months; 1 lived nine months.

Meissner[8] (pathologist at the New England Deaconess Hospital), however, believes that many gastric cancers are being resected early so far as lymph node metastases are concerned, but that other evidence of malignant spread is of equal importance in determining the ultimate survival of the patient. These observations of Meissner were made in the New England Deaconess Hospital, Laboratory of Pathology, where all the resected gastric specimens of this clinic undergo careful pathologic examination. He studied 100 resected specimens of carcinoma of the stomach and believed that other factors than metastasis to lymph nodes are of great importance in determining the ultimate course of gastric cancer. These factors, he has suggested, are diffuse lymphatic invasion (Fig. 2) through the various layers of the stomach,

FIG. 2

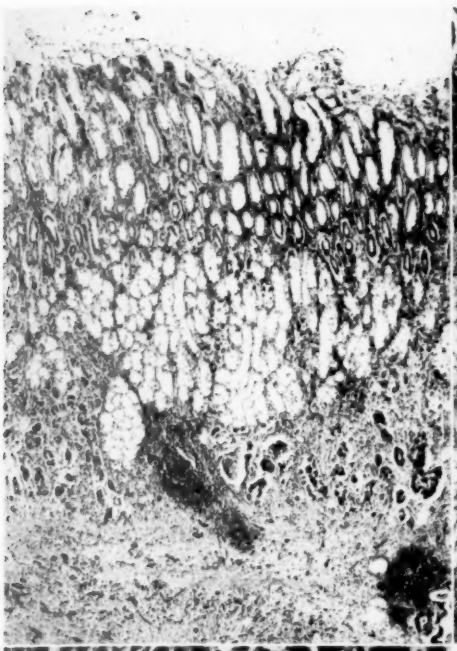
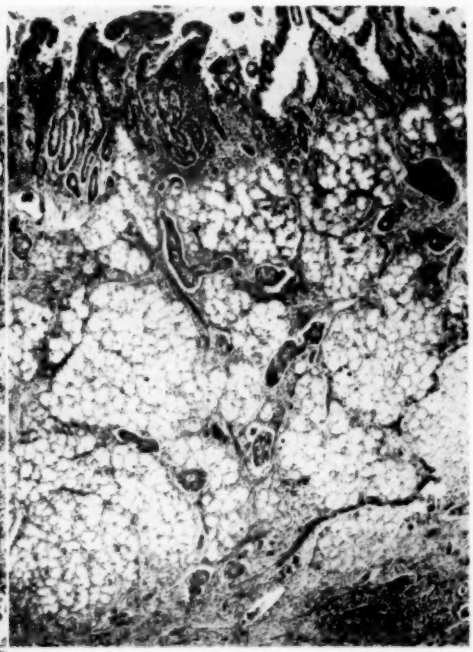


FIG. 3



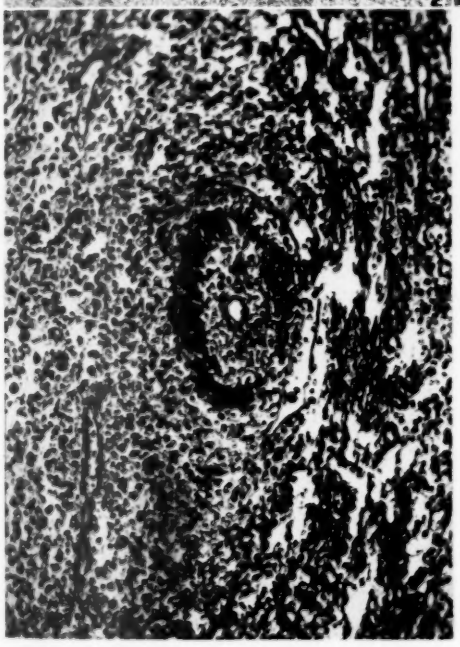


FIG. 4

FIG. 2.—Diffuse lymphatic spread in gastric submucosa. Note overlying mucosa is intact and uninvolved. (By courtesy of W. A. Meissner, M.D., New England Deaconess Hospital, Laboratory of Pathology.)

FIG. 3.—Invasion of duodenal mucosa with carcinoma from the stomach. (By courtesy of W. A. Meissner, M.D., New England Deaconess Hospital, Laboratory of Pathology.)

FIG. 4.—Gastric carcinoma growing within blood vessel; elastica of vessel is stained black. (By courtesy of W. A. Meissner, M.D., New England Deaconess Hospital, Laboratory of Pathology.)

and involvement of the duodenum (Fig. 3) and blood vessel invasion (Fig. 4). He found blood vessel invasion present in 57 per cent of the cases and this vascular infiltration showed no relation to the extent of involvement of lymph nodes. He was impressed with the frequency of diffuse lymphatic spread which will take place with little demonstrable lymph node involvement and may not be recognized grossly. That this lymphatic spread may extend across into the duodenum as well as above the proximal line of resection (Table IX) in subtotal gastrectomy has not been sufficiently emphasized (Fig. 5).

Coller, Kay and McIntyre,[2] in a study of lymphatic invasion in 53 cases, found that the gastric carcinoma had involved the duodenum in 26.4 per cent.

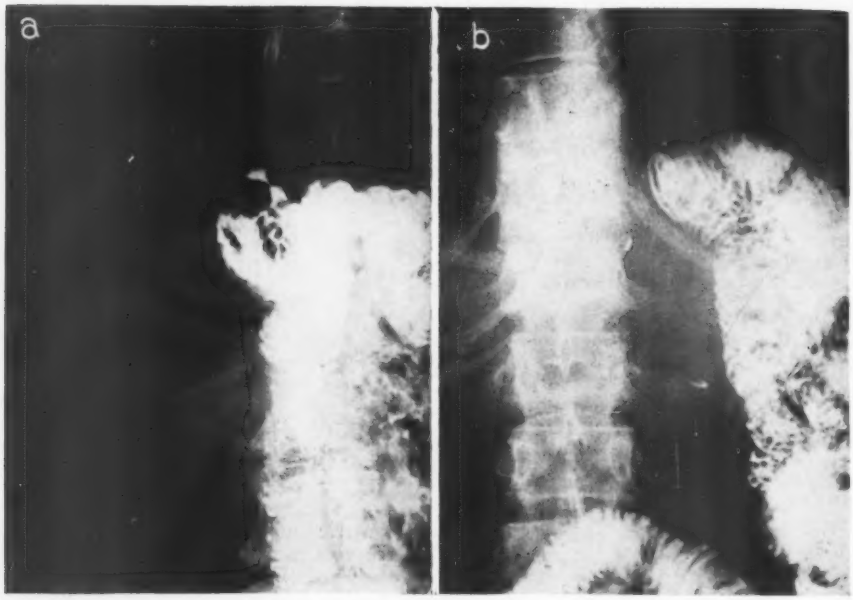


FIG. 5.—Esophagojejunostomy. (a) One and one half years after total gastrectomy. (b) Same patient two and one half years after operation. Patient is alive and well. Tumor was carcinoma simplex with extension by lymphatic spread; most of the nodes were involved.

The upper margin of the extension of the gastric cancer in their group could not be determined by gross appearance alone.

Castleman[1] has also emphasized that submucosal lymphatic invasion may extend across the pylorus and involve the duodenum as well as to the proximal level of the gastric resection in subtotal gastrectomy. He reported 21 cases of gastric carcinoma in which invasion of the duodenum varied from 4 to 23 mm. beyond the pylorus. It is possible frequently, then, when subtotal gastrectomy is done, to find neoplastic tissue microscopically at both margins of the surgical resection, upper and lower, in what usually appears as normal tissue beyond the gross neoplasm. In our group of 127 patients with gastric neo-

plasms treated by total gastrectomy, such diffuse submucous lymphatic spread was noted in 12 cases (9.5 per cent) in which extension of the carcinoma near or through the line of resection was found microscopically in spite of the fact that the level of resection of the stomach had been carried through apparently grossly uninvolved tissue. Of the 12 cases with such diffuse lymphatic spread there were, as would be expected, three postoperative deaths, and two patients lived less than six months; four lived six months or more; only three patients survived longer than nine months, one for a year, one for a year and a half and one for two years. It is to be remembered that practically all of these 127 patients in this series in whom total gastrectomy was done had very advanced lesions and that when the operation is limited to such advanced lesions, submucosal spread will frequently be encountered.

Shields Warren[15] has reported 23 instances (19.6 per cent) of recurrent carcinoma in the gastric stump in autopsies on 122 patients who subsequently died from recurrent disease following partial gastric resection for malignancy. While it is conceded that a wide margin of normal gastric wall and duodenum should be included in gastric resection for carcinoma of the stomach, if this

TABLE X.—*Total Gastrectomy—139 Cases.*

		Patients
*A	Total gastrectomy with splenectomy and jejuno-jejunostomy	63
B.	Total gastrectomy with splenectomy	33
C.	Total gastrectomy with jejunojejunostomy	23
D.	Total gastrectomy only	20
		139

*5 patients in Group A had resection of adjacent viscera—colon, pancreas, liver—with 1 death.

submucosal spread can occur in what appears to be normal duodenal or stomach wall, how can one ever be sure of the safe line for resection in partial gastrectomy? Partial gastrectomy is obviously not an extensive enough resection to offer the best chance of removing all of the malignancy in the greatest possible number of cases of gastric cancer.

From time to time we have published our methods of doing total gastrectomy, and many points regarding the technic of total gastrectomy have been published by many others. How one does it is not as important as the adequate removal of the gastric malignancy together with all of its involved lymph nodes. Coller, *et al.* and Meissner have shown that it is not enough to remove only palpable nodes or enlarged nodes but that all lymphatic drainage areas of the stomach should be included in the resection, something which we believe can be accomplished only by a total gastrectomy, which should include splenectomy.

THE EXTENT OF THE OPERATION

If total gastrectomy is to be applied to cancers of the stomach early or late it should be of the most radical type (Table X). To fill this requirement

it should include the removal of the duodenum at the lowest possible level without involving the point in the duodenum where the common duct enters it. Since, as already stated, submucosal spread onto the duodenum is not uncommon and one will not know the extent to which this spread has taken place until a specimen is examined microscopically, radical removal of the duodenal stump to the lowest possible level is an important step in the

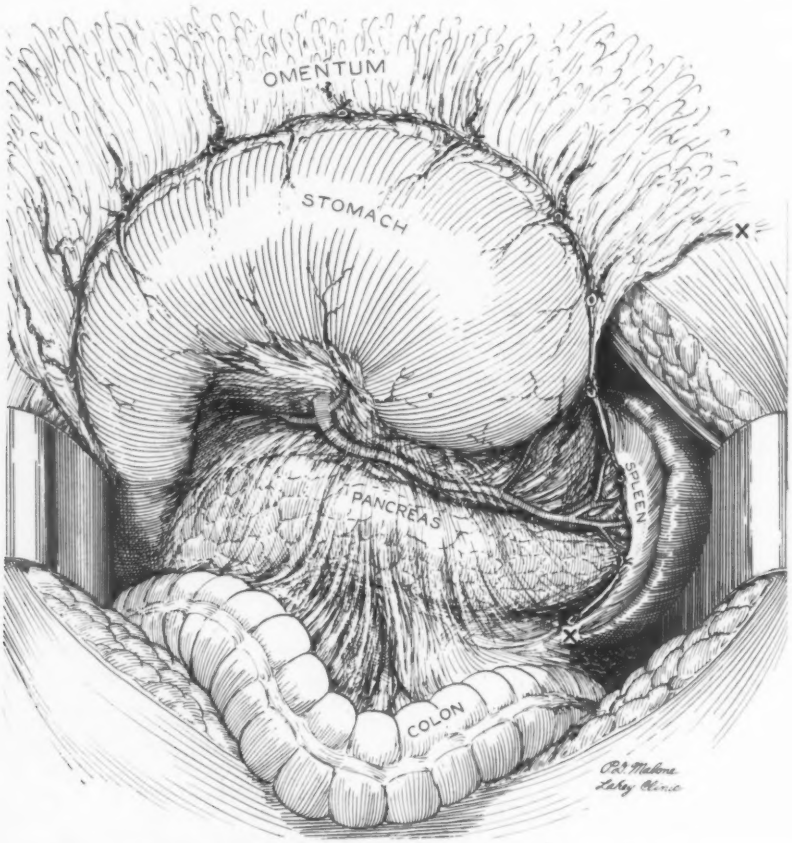


FIG. 6.—This drawing illustrates complete detachment of the omentum from the colon and stomach turned up to visualize completely the lesser peritoneal cavity. In cases in which operability is doubtful this exposure makes it possible to decide operability or inoperability of the lesion. If the lesion proves inoperable because of its demonstrated spread, the operation can still be terminated even at this point with no ill effects. (From Surg. Clin. N. Amer., **29**: 747, 1949.)

accomplishment of this aggressive procedure. All of the gastrohepatic omentum, attached to the lesser curvature, should be carefully removed with the stomach, after the gastric artery is tied as close to its origin as possible. The great omentum should be separated carefully from its point of origin on the hepatic flexure to well past the splenic flexure and up to the lower pole of the spleen. The spleen should be included with the stomach because of the

drainage of the lymphatic channels along the greater curvature into the group of nodes in the omentum between the greater curvature and the splenic hilum, as shown in Figure 1. The chain of nodes running on either side of the esophagus up into the hiatus in the diaphragm should be carefully wiped down, all of the vagus fibers cut, and the wall of the esophagus carefully wiped downward to free it of the lateral chain of nodes, as shown in Figure 1, attached to it. The esophagus should be mobilized well down from the hiatus after the vagus fibers have been cut, and frequently a distance of 10 to 12.5

FIG. 7

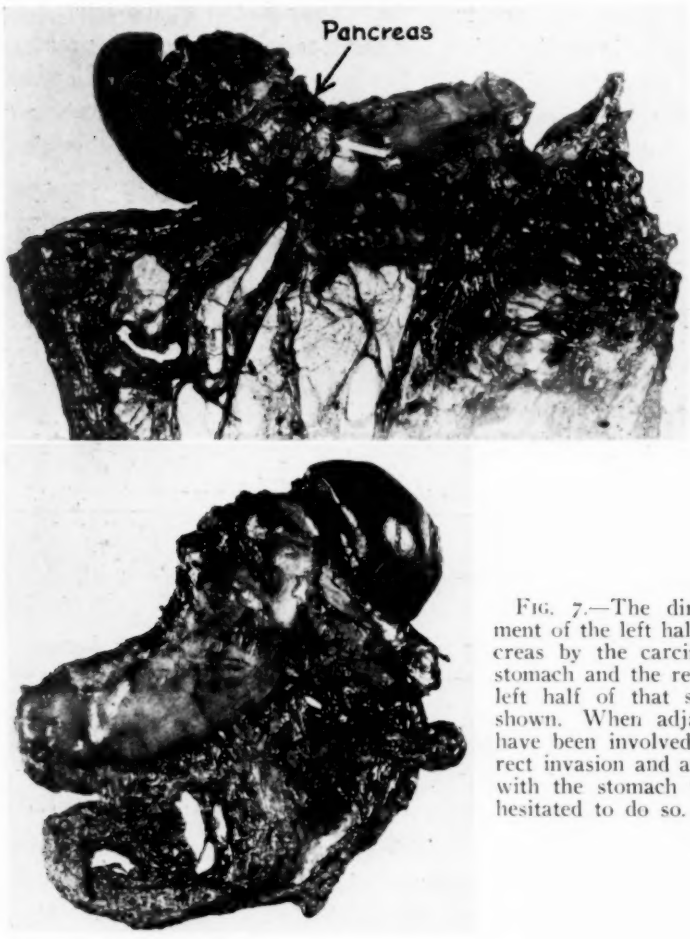


FIG. 7.—The direct involvement of the left half of the pancreas by the carcinoma of the stomach and the removal of the left half of that structure are shown. When adjacent organs have been involved only by direct invasion and are removable with the stomach we have not hesitated to do so.

FIG. 8

FIG. 8.—Entire stomach removed with omentum and spleen. Patient lived seven years and died of recurrent carcinoma. This specimen demonstrates that total gastrectomy fulfills the requirements for a really radical operation for cancer of the stomach. It removes all of the involved organs, a good section of the duodenum, the gastrohepatic omentum, the spleen with the group of nodes between it and the greater curvature and all of the node-bearing great omentum.

cm. of esophagus can be so mobilized. With such an extensive removal of the stomach and its adjacent node-bearing area, a really aggressive and radical operation for cancer can be done.

One of the important steps in the employment of total gastrectomy for gastric cancer is the determination of operability. This can best be accomplished by a series of investigations performed in sequence. When the abdomen is first opened, one can, particularly in advanced lesions, settle inoperability merely by palpating the lesion, as when the lesion is firmly fixed and when there are obvious metastases to the liver. In less extensive lesions, however, the determination as to whether or not total gastrectomy in such a case is justifiable is often not easy to settle. If the lesion seems operable, the first step is to investigate the pelvis for the possibility of gravity metastases and if they are present, obviously further steps in the procedure are unjustified. If the pelvis is negative, the next step is to turn up the transverse colon and inspect its root in the jejunal fossa. Not infrequently, even though the lesion

TABLE XI.—*Survival—37 Cases of Carcinoma; Splenectomy Not Done.*

	Cases	
Postoperative deaths	15	
Lived less than 6 months	2	
Lived 6 to 12 months	2	
Lived 1 to 2 years	9	
Lived 2 to 3 years	1	
Lived 3 to 4 years	2	
Lived 5 or more	5	14%
	36	

These were the earliest cases done before splenectomy was routinely employed.

from the front view and from palpation seems operable, with this exposure it will be found to have invaded the mesenteric root to such an extent that continuation of the procedure will be unwise. If the lesion has not involved the root of the transverse mesocolon, one next separates the omentum from the transverse colon as shown in Figure 6, so that the entire lesser peritoneal cavity is exposed. In those cases in which there is doubt as to the wisdom and justification of employing total gastrectomy in cancers of the stomach, there is no single step by means of which one can settle whether or not total gastrectomy can be wisely employed which is comparable with complete separation of the omentum and the transverse colon and the complete exposure of the entire lesser peritoneal cavity. With this exposure, should the lesion be demonstrated as extending into the pancreas and beyond, one can terminate the operation by dropping the omentum back into the abdomen and leaving the lesser peritoneal cavity widely open with no disadvantage. With this exposure, invasion of the pancreas can be demonstrated and feasibility of resecting the tail and body of the pancreas when it is involved by direct contact with the lesion can be demonstrated (Fig. 7). When the lesion is in the prepyloric

region and has involved the head of the pancreas it can be plainly demonstrated and its inoperability clearly determined. With this wide exposure and with the stomach turned up, the extent of involvement of nodes around the celiac axis and into any retroperitoneal tissue can be plainly demonstrated.

In our early cases of total gastrectomy, no attempt was made to remove the spleen or to do a jejunojejunostomy (Table XI). Our present-day plan consists not only in the wide removal of all involved lymph nodes but also in the removal of the spleen (Fig. 8) and the performance of a jejunojejunostomy to prevent the bathing of the esophagojejunal anastomosis with the bile and pancreatic juices, which often results in the production of an esophagitis with dysphagia and substernal pain.

We wish particularly to call attention to a procedure developed by one of us (S. F. M.) by means of which it has been possible to leave in place a soft, indwelling Penrose tube (Fig. 9) through which the patient can be fed for the first few days after operation. As can be seen in this illustration, the Levin tube which is passed through the anastomosis is brought down to the point where the entero-enterostomy is done, the Penrose tubing is tied to the end of a Levin tube, and the Levin tube, as it is withdrawn through the nose, pulls the soft Penrose tubing through with it, leaving thus a small, hollow tube of soft rubber, nonirritating to the nose, through which fluids and food can be introduced.

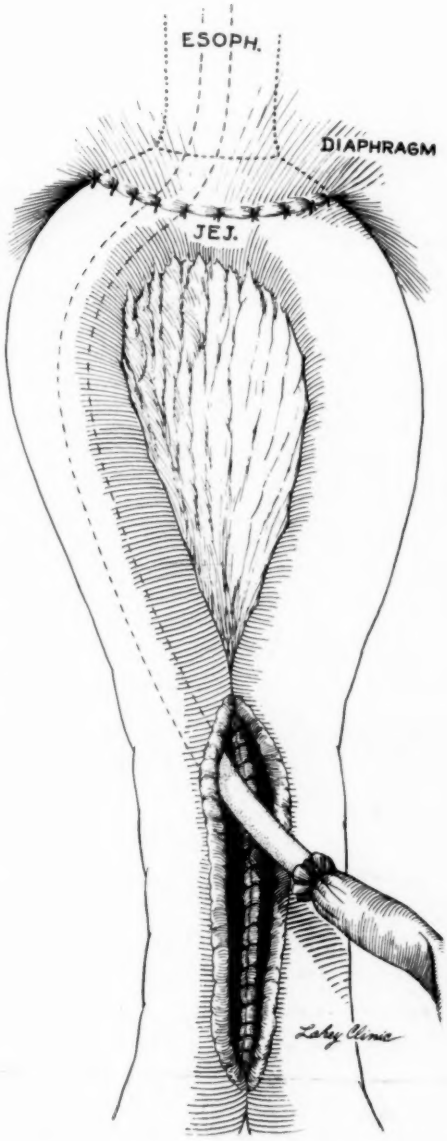


FIG. 9.—Esophagojejunostomy and entero-enterostomy. Note thin rubber Penrose tubing tied to the lower end of the Levin tube to be withdrawn through esophagus and out of the mouth to permit early feeding, thus making jejunostomy unnecessary.

MORTALITY

From 1927 to 1943 there were 75 cases of total gastrectomy, with 26

deaths, an operative mortality of 34.6 per cent. Since 1944 to the present date there have been 64 total gastrectomies with six postoperative deaths, a mortality of 9.4 per cent. The cause of death in each group is given in Table XII. It is relevant that postoperative death in the majority of cases in the first group was due to sepsis, such as mediastinitis, peritonitis or pneumonia; 22 of the 26 deaths (85 per cent) were on the basis of some type of sepsis. In the group of cases since 1944 in which the mortality has been so markedly decreased, only two of the six deaths were due to sepsis or peritonitis.

TABLE XII.—*Total Gastrectomy—139 Cases; Causes of Postoperative Deaths.*

Cause of Death	Cases	
1944–1950—64 Patients—6 Deaths		
Embolism	1	
Peritonitis	2	
Cardiovascular disease	3	
	6	
1927–1943—75 Patients—26 Deaths		
Cardiovascular disease	3	
Embolism	1	
Mediastinitis	2	Sepsis, 22
Peritonitis	17	
Pneumonia	3	
	26	

TABLE XIII.—*Total Gastrectomy: Carcinoma—127 Cases.*

	No Metastases in Lymph Nodes 44 Cases (34.6%)			Metastases in Lymph Nodes 83 Cases (65.4%)		
	Living and Well	Alive with Recurrence	Dead	Living and Well	Alive with Recurrence	Dead
Postoperative deaths			12			19
Survived						
Less than 12 months	5	1	4	4	..	27
1–2 years	3	..	3	2	1	17
2–3 years	2	..	2	1	..	3
3–4 years	..	..	2	..	..	2
4–5 years	2	..	..	1	..	2
5–6 years	2	..	2	1	..	..
6–7 years	..	..	1	..	..	..
7–8 years	1	..	..	..	..	..
8–9 years	..	..	..	..	..	..
9–10 years	..	..	..	2	..	..
10–11 years	..	..	..	..	..	..
11–12 years	1	..	..	..	1	..
12–13 years	1	..	..	..	..	..
	17	1	26	11	2	70

Tables XIII, XIV and XV give the length of time that these patients with total gastrectomy for carcinoma have survived operation (Figs. 10 and 11). The survival rate is much less in those cases in which the lymph nodes were

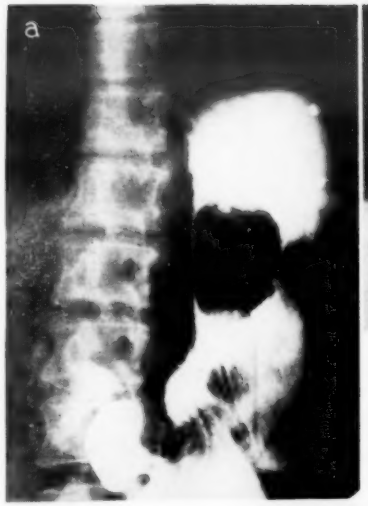


FIG. 10.—Total gastrectomy for malignant tumor; patient alive and well 13 years since operation: (a) prior to total gastrectomy; (b) esophagojejunal anastomosis.

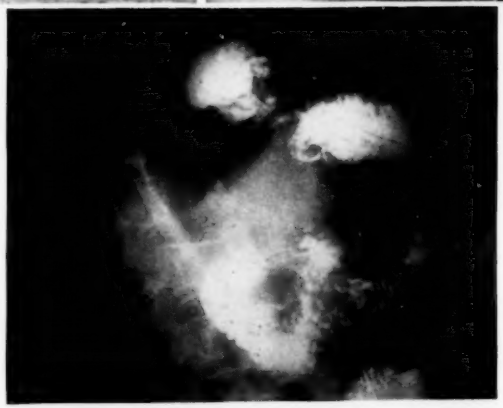
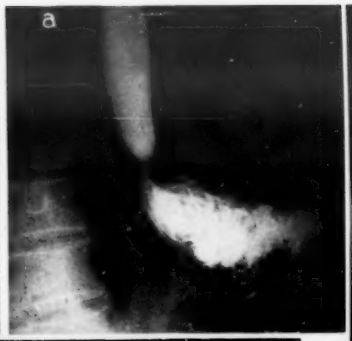


FIG. 11.—Esophagojejunostomy; total gastrectomy performed for carcinoma simplex. Patient alive, well and working ten years after operation.



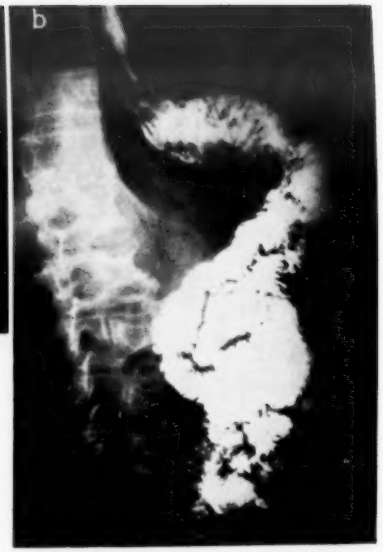


FIG. 12.—Esophagojejunal anastomosis after total gastrectomy for malignant tumor. (a) Contraction and obstruction of lower end of esophagus at anastomosis; (b) after dilatation of the obstruction. Patient is well; no dysphagia present.

involved than in those cases in which there were no nodal metastases (Table XIII). Of the 127 patients, 33 out of 83 patients (40 per cent) with involvement of lymph nodes survived one year or more, whereas 22 of 44 patients (50 per cent) with negative lymph nodes lived one year or more. It must be recalled that these figures were obtained in those cases of cancer of the

TABLE XIV.—*Survival After Total Gastrectomy for Cancer (127 Cases).*

	Cases
Postoperative deaths	31
Survived	
Less than 1 year	41
1 to 2 years	26
2 to 3 years	8
3 to 4 years	4
4 to 5 years	5
5 years or more	12
	127
21.9 per cent lived 3 years or longer	
12.5 per cent lived 5 years or longer	

stomach in which the lesion was too advanced for partial gastrectomy and in cases which in the past had been considered relatively hopeless. Twelve patients of the group of 55 (22 per cent) surviving one year were alive and well five years or more following total gastrectomy. While this salvage rate is low, it is not uncheering in such an advanced group of cases, and it is not unreasonable to anticipate improvement in these figures if this radical surgery is attempted in early gastric carcinoma.

TABLE XV.—*Patients Now Living After Total Gastrectomy for Cancer.*

	Cases
Less than 12 months	10
1 to 2 years	6
2 to 3 years	3
4 to 5 years	3
5 years or more	9
	31

In the light of the figures presented in these tables and as a result of this not inconsiderable experience with total gastrectomy, largely in patients with advanced malignancies of the stomach, it does not seem unreasonable to suggest that we may very well improve our results if this operation of total gastrectomy is employed in the earlier forms of malignant diseases of the stomach, in a comparable way, as radical procedures are employed in cancers of the rectum, the colon, the thyroid and of the breast. As one of us has stated in an editorial[6] (F. H. L.), with such a radical approach one has everything to gain and, in view of the present low five-year survival rate, very little to lose. As

pointed out in this editorial, total gastrectomy is a difficult operation, requiring anastomosis of the jejunum to the esophagus under the ribs where accurate suture requires great care and gentleness. It is an operation that requires adequate and complete relaxation which can be obtained only by good anesthesia. It is an operation often quite shocking in character and one which must be done on patients some of whom are fat and some of whom are in poor states of nutrition. It is for this reason that we feel obligated here to repeat a warning which was included in the aforementioned editorial, namely that it will require considerable discrimination on the part of surgeons operating upon patients for cancers of the stomach as to their capacity to apply this operation to patients with early cancer of the stomach, the place where, as we have suggested, this procedure has the greatest possibility of improving our quite unsatisfactory results obtained with the less radical procedure of subtotal gastrectomy.

There are some real problems which result from the complete removal of the stomach, but these are not insurmountable. Life can be satisfactory without a stomach, patients can be comfortable, can have a feeling of physical well-being, can eat reasonably well and attain a reasonable economic status. One must expect some difficulties in nutrition in these cases. We doubt if a patient can ever become obese after a total gastrectomy and sometimes thin individuals have had a quite difficult time in gaining weight or even in maintaining their weight. Most of them have had a fair appetitie but are quickly satisfied with a small amount of food, or may develop slight discomfort while eating which causes them to limit their food intake. The principle of frequent feedings of comparatively small amounts of high caloric foods is the obvious answer to this particular problem. These patients are advised to follow a six-meal schedule rather than a three-meal schedule.

Because of the loss of the macerating or softening process normally performed by the stomach, some attention must be given to the physical character of the food eaten. If the patient has good teeth and is careful to chew his food, usually it is not necessary to do much more about this aspect of the diet. Patients who have poor teeth and who are likely to eat hurriedly should eat food which is mechanically finely divided and is reasonably soft in texture so that it can be readily accepted by the jejunum.

Some of these patients, as would be expected from this rearrangement of the alimentary tract, are troubled by the well known "dumping" syndrome and symptoms develop, such as excessive fullness, a sense of weakness, sweating, nausea and palpitation which occur immediately after ingestion of food. This has best been managed by frequent small feedings with attention to the limitation of fluids. Usually solid food is better tolerated than fluids, and cold liquids are particularly likely to bring about distress. These patients obtain considerable relief from these symptoms by lying down for a few minutes immediately after eating. We have not considered it rational to give these patients hydrochloric acid because they do not have any pepsin to be activated

by the acid. We have not been convinced that it is necessary to give them any pepsin or any digestant to take the place of the loss of gastric juice so far as digesting the food is concerned.

Some of these patients following total gastrectomy occasionally experience some dysphagia and difficulty with eating, due apparently to narrowing and spasm of the esophagojejunal stoma, and some of them have had to have dilatations done by bougie. Some patients even without demonstrable obstruction have had periodic episodes of dysphagia and regurgitation of esophageal mucus. It has, at times, been a troublesome complication. If definite obstruction is shown to be present by roentgen examination of the esophagus or by esophagoscopy, dilatation by bougie can readily be done and will in most instances correct the dysphagia (Figs. 12 and 13). In this group of 139 cases in which total gastrectomy was performed, dilatation of the opening of the esophagus into the jejunum was necessary in 42 patients. One should not conclude because of swallowing difficulty or dysphagia that the patient has recurrent carcinoma. To establish the presence or absence of recurrent carcinoma at the esophagojejunal anastomosis, when obstruction occurs esophagoscopy can be done and a biopsy specimen obtained after dilatation.

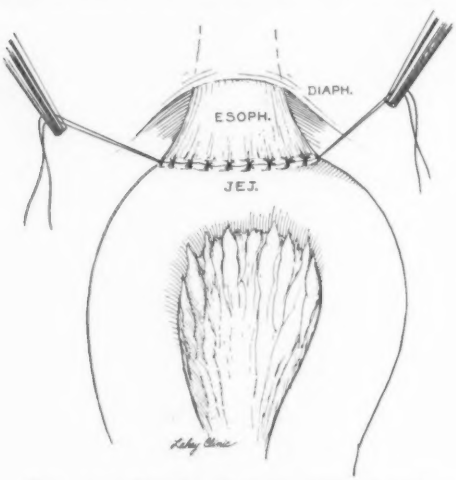


FIG. 13.—Esophagojejunostomy. Traction sutures are placed at angles of anastomosis to prevent narrowing during suturing of jejunum to esophagus. This trumpets the end of the esophagus and serves to prevent later stenosis and obstruction.

The hematologic complications that arise following total gastrectomy vary considerably from patient to patient. The most common early postoperative manifestation—and very often this may take several years to develop—is a hypochromic state due to an iron deficiency. This is easily treated with normal therapeutic doses of ferrous iron. At a somewhat later stage after total gastrectomy a macrocytic megaloblastic type of anemia may develop which readily responds to treatment with liver extract. Sometimes these two types of anemia may develop simultaneously and occasionally the macrocytic form of deficiency will develop before the iron deficiency state. In either case, the true type of anemia can be readily established by laboratory studies, and the proper treatment can be instituted. The accompanying chart (Fig. 14) illustrates the development of the hypochromic iron deficiency state, followed somewhat later by a macrocytic type of anemia in a patient who had total gastrectomy. This patient has now lived twelve and a half years since total gastrectomy for a malignant tumor, and could be followed only at quite irreg-

ular intervals because her home was at such a distance that she could not easily come to the clinic for examination and treatment. She did not, moreover, completely cooperate with her home physician. Since she has followed the full regimen under his care and has been examined at occasional intervals in the clinic, no further anemia has developed.

Farris, Ransom and Coller[3] have made significant observations which are of aid in correcting some of the difficulties following total gastrectomy. They stated that the stomach does not play an essential role in the digestion of

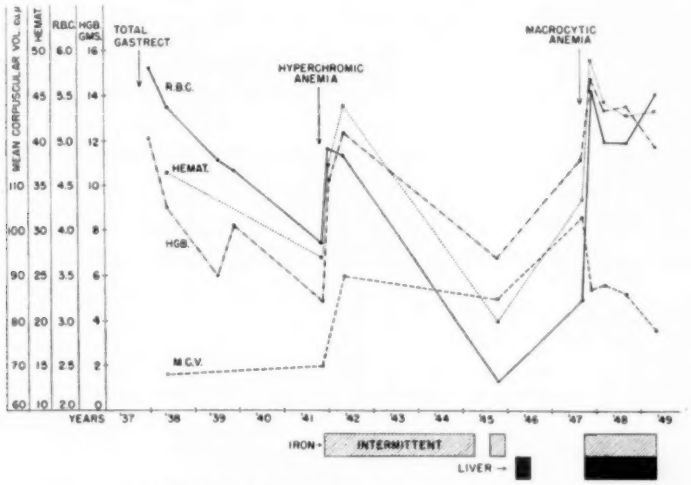


FIG. 14.—Hematologic data following total gastrectomy. Note the slow development of hypochromic anemia following operation, with normal response to medication with iron. Years later a macrocytic anemia developed; the blood picture rapidly returned to normal following therapy with liver and iron.

fats and protein, but that the absorption of glucose is more rapid than normal. They concluded that a high protein, low carbohydrate diet is helpful in preventing abnormalities. However, it is evident after experience with a very large group of patients following total gastrectomy that these patients are able to maintain reasonable weight, to eat quite satisfactorily and to have a reasonably comfortable existence and feeling of well-being.

CONCLUSIONS

One hundred and thirty-nine cases of total gastrectomy are reported of which total gastrectomy was done for malignancy in 127 and for extensive gastric ulcer or gastric ulcer involving the cardia or esophagus in 12.

Since 1944 the mortality has been significantly reduced (9.4 per cent) and is now comparable to the mortality associated with partial gastrectomy for gastric neoplasm.

In view of the tendency of gastric malignancy not only to spread to adjacent lymph nodes but also to invade blood vessels and to show diffuse

submucosal lymphatic spread in the gastric and duodenal wall well beyond the gross tumor, it is our belief that it is now time to suggest the employment of total gastrectomy in an increasing number of cases of cancer of the stomach, particularly in the earlier cases, if we are to improve the five-year survival rate in this field of malignant disease.

It is suggested that considerable discrimination in the selection of the cases for total gastrectomy is necessary and that the surgeon who undertakes a total gastrectomy must carefully weigh some of the following factors before proceeding with it: his technical skill and surgical experience, the quality and character of the anesthesia, the capacity of the patient to endure such a long and trying operation and the surgeon and his associates' ability to deal with the changes in conditions which will inevitably be associated with such extensive operations.

Patients following total gastrectomy are able to maintain a reasonable state of health, eat satisfactorily and carry on a comfortable existence. It will be necessary in many of these patients to maintain strict control of their diet and blood picture for long periods of time after operation.

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DISCUSSION.—DR. ARTHUR W. ALLEN: This presentation of Drs. Lahey and Marshall seems to me to be of utmost importance, not only to this Association but to surgeons throughout the world. There is a growing tendency to operate on cancer of the stomach in a more radical fashion than we have in the past. I thought this problem through to some extent, and it seems to me that it resolves itself into three categories: First of all, that of mortality; secondly, that of morbidity; and, thirdly, that of cure.

It will probably take a considerable length of time for the average surgeon of this country to approach the mortality rate as shown by Dr. Lahey and Dr. Marshall in their last 75 cases, because it is an extremely good record. I believe that throughout the country, if we were to analyze all patients who have had total gastrectomies the mortality rate would certainly be considerably higher than their figure. This may be partly explained by the fact that most of the total gastrectomies done are for disease so widespread that nothing short of this procedure would have included all visible disease. If, however, we are willing to subject younger, better risk patients, with smaller lesions, and less spread, to the total gastrectomy, in the hope that we may cure more of them, we undoubtedly can lower this mortality rate appreciably.

The second phase of the problem that I wish to stress is morbidity. We have all seen these patients who had their entire stomach removed—and, perhaps, a lot of adjacent organisms—who were able to maintain a good and satisfactory state of nutrition, but I am sure that you have also seen many patients who finally died after, perhaps, one or two years, where autopsy showed no sign of recurrence whatever, and who had not had a single happy day following their operation.

Whether that feature can be overcome or not, I don't know, but I certainly believe at the moment—in average hands, at least—that this very serious objection to total gastrectomy must be considered in all cases of carcinoma.

Now, as to the question of the cure rate, that, of course, should be our primary object, and I am the first to admit that subtotal gastrectomy for carcinoma of the stomach, even though it be extensive, is not a good cancer operation as we ordinarily consider such a procedure as it applies to the other structures in the body.

On the other hand, when Dr. Claude Welch and I analyzed the recent ten-year experience in cancer of the stomach at Massachusetts General Hospital—having in mind this very possibility of a more radical attack—it was very interesting to us to find that when the patients did die of recurrence following subtotal resection, with removal of the omentum, with removal of a part of the duodenum, and sometimes a fairly adequate glandular dissection in the region of the left gastric vessels, they did not develop their return of disease in the stomach itself, or in a region which we felt might have been removed by more radical original procedure. I think one must take these factors into consideration.

Although the salvage rate in this group of patients is only 21 per cent of those who could be subjected to resection—and it might very well be elevated to some extent by total gastrectomy—we feel at the moment that the morbidity and mortality associated with total gastrectomy may offset this radical attack. It is well known that patients with lymphosarcomas of the stomach are much more apt to live five years and longer than those with adenocarcinoma.

DR. OWEN H. WANGENSTEEN: I have a feeling that we have need of better classification of cancers than we have. In gastric cancer most of us have followed the so-called Borrmann classification, which relates only to the extent of the cancer on the mucosal surface. In the Dukes' classification of rectal cancers, one speaks of the extent of penetration and whether or not there is coincidental involvement of the lymph nodes.

I think we have need of a classification in which the factors of size, penetration, the status of the lymph nodes and the absence or presence of other areas of involvement can readily be indicated. By employing the following designations: A for size; B for extent of penetration; C for status of the lymph nodes; and D for areas beyond,

such as liver, lung and bone, it is possible, with the concomitant use of the factors 0, 1, 2, 3, and 4 and a drawing of the organ with the location and size of the neoplasm drawn into convey to all, including medical students, an intelligible future of the existing situation. Certainly, more uniformity is necessary in our language of classification concerning cancers. I have the impression that a scheme of the sort depicted in the accompanying slide would meet some of the requirements of greater uniformity, at the same time being adaptable to cancers in any organ.

Now, there is a facet to the problem of cancer extirpation which I think deserves more important consideration than it has had in this discussion: That question concerns the lymph nodes. When this Association met a year ago, I said that we were just then beginning to explore the idea of so-called "second-looks" in patients with positive lymph nodes. (Tr. Am. S. A., **67**: 219, 1949; also Wisconsin M. J., July, 1949.) Now, whether it concerns cancer of the breast, the stomach, colon or rectum, we know that the really important item in cancer surgery of any of these organs, is "Were the lymph nodes free, or were they involved?" It is a tragic circumstance that, approximately 75 per cent of all cancers of any organ exhibit lymph node involvement when the patient presents himself for treatment. It is, of course, a corollary of late diagnosis. To recognize a cancer when symptoms are present, or a lump is palpable, suggests, for most cancers, that the cancer is probably already of two years duration. Therefore, in cases of alimentary tract cancer and especially in patients with colic, rectal or gastric cancer, when the lymph nodes are found to be involved, we propose to the patient that we take a "second-look" after the elapse of approximately six months after the initial operation. The extirpation of cancer is very much like the eradication of quack grass. You cannot do a complete and thorough job in one sitting. When the field is surveyed a few weeks after the initial effort, surviving quack grass sprouts can be seen here and there still. And so it is, too, in the lymph node positive cancer cases.

We have done "second-looks" upon 16 patients with colic and rectal cancer who had metastatic cancer in the regional lymph nodes. Eleven showed residual evidence of cancer, that is 68 per cent. In two patients in this group we have taken two third "second-looks." One of these now is negative; I regard her as cured; the other is still positive. We already have her permission for a fourth "second-look." The residual cancer in both these patients was finally concentrated in a few peri-aortic lymph nodes

It is difficult to remove all the potential lymph node bearing tissue the first time; one must, of course, set himself the task of trying to do it well anatomically. I have done two "second-looks" upon patients with gastric cancer who were asymptomatic. When the second operation was done, one of these patients had two cancerous lymph nodes at the time of the "second-look" operation; one was on the hepatic artery, the other behind the duodenum. I have the feeling that a second "second-look" will succeed in controlling the situation. One "second-look" must be negative before it is safe to call a lymph node positive case cured. This latter patient already has consented to a second "second-look." The cooperation of patients in this venture has not been lacking, and, of course, we have been modern enough in our views to inform patients when they have cancer. Patients do respond well to manifest evidences of sincerity in their surgeons. Moreover, I would like to add that I believe this is going to become an important activity of the surgeon in the management of cancer.

In patients with diffuse gastric cancer, total gastrectomy obviously is a necessity. In most gastric cancers, as in cancers generally, the lymph nodes constitute the most important concern of the surgeon, when they are involved. In such patients, the principle of the "second-look" operation is in order. A "second-look" in which no residual cancer is found is synonymous with cure. That circumstance offers hopeful reassurance.

I have returned to a mid-line supra-umbilical incision adding a median sternotomy, cutting out extra pleurally into the left fourth interspace. This maneuver together with cutting of the crura provides excellent exposure. I have removed 9 cm. of esophagus during total gastrectomy without opening the pleura through such an approach. And

in cardiospasm with a tortuous boot-shaped esophagus, 14 cm. of esophagus has been removed easily through the abdomen. It may well be that by extending the sternotomy into the second interspace on the right side, one might be able to remove a cancer in the mid thoracic esophagus, placing the stomach in the anterior mediastinum, establishing the anastomosis with the esophagus just above the superior vena cava.

We are now excising the spleen regularly in all operations for gastric cancers, because there are lymph nodes in the gastrosplenic omentum as the studies of Coller and his associates indicated (Arch. Surg., **43**: 748, 1941). Excision of the splenic artery to the celiac axis makes it practical to remove the suprapancreatic lying lymph nodes.

DR. JOSEPH E. STRODE: I have always been somewhat confused as to the relationship of a salubrious climate to a disease and infection. Dr. Holman brought that up with the situation out in California, and I would like to say that if disease depended on a salubrious climate, I believe there would be very little need for the medical profession in Hawaii.

I have been interested in this subject of carcinoma of the stomach in Hawaii because, as you may or may not know, 40 per cent of our population are Japanese, and we have found—in a recent analysis of some 200 carcinomas of the stomach that I have explored—that the incidence of carcinoma of the stomach in the Japanese race is approximately twice that found in other races. For this reason we have been very acutely aware of the potential possibilities of ulcerating lesions of the stomach in Japanese men particularly.

Some years ago we made up our minds that we would never advise an Oriental with an ulcerating lesion of the stomach to be treated expectantly. As the years have gone by, we have gradually included all races in that category.

I do not think that total gastrectomy necessarily carries any higher rate of mortality than the usual subtotal gastric resection.

In this series the subtotal gastric resections had a mortality of 16.5 per cent, and in 21 total gastrectomies the mortality was 10.5 per cent.

While I have not had the experience of Dr. Lahey or Dr. Wangensteen, I do believe that the ordinary operator doing gastric surgery can keep the mortality of total gastrectomy down within reasonable limits.

I would like to say that in traveling about the country and speaking with many men, and reading the literature, there seems to be a number of people who still believe that ulcerating lesions of the stomach should be given a course of medical treatment. I am sure it has been your experience, as it has been ours, that you have had patients in days gone by who had small lesions whom you advised that they be treated medically; they got better and disappeared from view, and then came back within the course of a few months with an entirely inoperable lesion.

Recently we had a Japanese man come to us who had been diagnosed five and one-half years ago as having a small ulcerating lesion on the lesser curvature; we had advised surgery. He came back, and had a normal gastric analysis. He had what looked like a benign lesion, but in view of the fact that we had that previous experience with him, we advised him to have a radical resection. He had an inoperable lesion.

When you consider the safety of gastric resection in such cases against the danger of perforation and hemorrhage, it seems to me there is no logical reason for not operating on all lesions of the stomach, regardless of age. We have been guilty for a number of years of treating a lot of these cases medically, but I am sure I am not going to advise anyone with an ulcerating lesion of the stomach to be treated expectantly.

MR. PHILLIP ROWLAND ALLISON, Surgeon-in-Charge of Department of Thoracic Surgery, University of Leeds, Leeds, England: The radical treatment of carcinoma of the stomach depends on an accurate knowledge of the lymphatic drainage. We

should be in a position to remove the growth with a margin of healthy tissue in continuity with the cellular tissue and glands concerned in its lymphatic drainage.

At a recent discussion in Oslo, Professor Holst made the pertinent remark that "There was no boundary to the lymphatic drainage of any organ, and that for the stomach it could be regarded as being somewhere about the thyroid cartilage." Whatever lymphatic dissection we perform, therefore, must of necessity be a compromise. The picture which Dr. Marshall showed of the lymphatic drainage of the stomach, was taken from Gray's Anatomy, and this was from the original description of the lymphatics of the stomach by Jamieson and Dobson in the "Lancet" in 1907. The picture shown, however, was only the front view, and this is deceptive. When the stomach is turned up so that its posterior aspect is seen, as in the second picture from Jamieson and Dobson, the lymphatic vessels are seen to pass in the retro-peritoneal tissue from the lesser curvature, the fundus and posterior aspect of the stomach directly into the glands and the hilum of the spleen and along the top of the pancreas. A radical operation, therefore, necessitates the removing of the body of the pancreas and the spleen with the retro-peritoneal tissue on the under aspect of the diaphragm in continuity.

One point which Dr. Marshall raised, but which has not been stressed enough, is that the lymphatic glands themselves are not the only important structures to be considered. The cellular tissue between the viscus and the lymphatic glands is equally important, and I would like to stress the necessity for removing this in continuity and not piecemeal. This applies particularly to that area of cellular tissue between the pancreas and the hiatus of the diaphragm.

I place great importance on the restoration of continuity by a length of jejunum on the Roux principle. The advantages of this are, firstly, that the esophagus does not suffer from reflux digestion by pancreatic and bilious fluid, as sometimes occurs after end-to-side anastomosis (and I think that stenosis of the esophagus, after total gastrectomy, is due to digestion and ulceration with fibrosis rather than bad suturing), and secondly, that with this method of anastomosis can be performed at any point in the mediastinum. If an end-to-side anastomosis to the jejunum is performed by drawing up a simple loop on its mesentery, then the resection of the growth will inevitably be performed with one eye on the possibility of the esophagus reaching the jejunum. This leads to resection of the esophagus too low down and too close to the growth. This second point, of course, is more important for growths at the upper end of the stomach than for those at the lower end.

Dr. Frank H. Lahey (in closing): We are well pleased to have presented this paper if for no other reason than the discussion it has prompted. It is obvious that this subject is being thought about by a great many people and also that a great many people are dissatisfied with the present situation in the surgical treatment of cancer of the stomach.

It is encouraging that everyone has noticed an increase in his operability rate, but we must realize another thing, another approach to this. We can never deal with this subject, no matter what surgical procedure we employ, until we develop methods of making earlier diagnoses. It is unfortunate that cancer of the stomach is a relatively silent type of disease and can never be comparable with cancer of the rectum and colon in which we can make a diagnosis with the proctoscope in 70 per cent of the cases. When one realizes the frequent lack of early symptoms and even the gastric quietness except for mild digestive symptoms, often in fairly advanced lesions, we know that we will always have difficulty in making a diagnosis of cancer of the stomach as early as we would like.

The purpose of this paper was not to report 140 cases of total gastrectomies but to suggest its availability as a more radical method of operating upon this lesion and to submit data on the operation of total gastrectomy. In 1927, when I reported our first 8 cases, it was a technical accomplishment, although Finney and Rienhoff had

reported 64 cases prior to that. It seems to me that it is of the greatest value to be able to say what the mortality rate is in a large enough group of cases so that one can assume that it is a reasonably accurate figure to present. Too, we can ask, "How well do these patients get on after operation?" Dr. Allen is largely right regarding difficulties in feeding these patients, although we do not feel as pessimistic as he does about the postoperative digestive difficulties. Also, the question, "What is the five-year survival rate" can now be answered.

The figures have been presented to you. At the time I wrote the editorial in Surgery, Gynecology and Obstetrics we could give only the three-year survivals. The five-year survivals are not so very encouraging, but we must remember that up to now we have employed this operation only in cases too advanced for subtotal gastrectomy. However, we can point to some results from this experience.

In the first place, the operation is not difficult to learn. It is technically difficult to do it at first, and it is technically difficult to do the anastomosis up under the edge of the ribs, but a quite rough type of anastomosis works well, particularly today with the antibiotics.

As to the patients who have constriction at the point of anastomosis, the last speaker has made what is probably a very pertinent suggestion in the management of these cases because all of these patients do get esophagitis. That was the reason that early in our experience we began to employ entero-enterostomy in the anastomosis of the jejunum to the esophagus to diminish the amount of irritating material—bile and pancreatic juice—which regurgitates up into the esophagus.

The patients who have some stenosis get along very well with dilatation. Our later survivals have relatively little trouble with this complication.

I believe it is going to require a great deal of courage to do the thing in cancer of the stomach that we do without hesitation in a cancer of the rectum. I have tried to preach over the years that if one were logical about cancer of the rectum he would say that the smaller the lesion, the more aggressive the surgical procedure because the greater the chance of cure.

It is probably going to require courage to do a total gastrectomy in the case of small gastric malignancies. On the other hand, we are never going to find out (and even then we will not find out for ten years or longer) whether or not this more aggressive and radical surgical approach to the problem is a wise one until we accumulate some data as to whether or not these procedures will improve on the one which is now so unsatisfactory, subtotal gastrectomy.

I hope this proposal will not stimulate men who are not experienced with this procedure to undertake it with any idea that it is simple. On the other hand, I would like to agree with Dr. Strode that any good surgeon, experienced with gastric surgery, and with good anesthesia and good help, can do this operation with comparable mortality figures. Dr. Marshall and I wish to thank all of the discussers for their kindness in commenting on this paper.

THE TREATMENT OF INGUINAL HERNIA IN INFANTS AND CHILDREN*

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IN THE VOLUMINOUS LITERATURE ON THE SUBJECT OF HERNIA, the basic principle of treatment of inguinal hernia in infants and children has received insufficient consideration. The reason for much misinformation concerning hernia in the early age group is quite understandable because most of the writing has been on hernia in adults. In textbooks and systems of surgery the problem of hernia in children is often dismissed with a few sentences, or the principles governing treatment in adults are unconcernedly applied to children.

The cause of indirect inguinal hernia during childhood is not muscular weakness but failure of the processus vaginalis to obliterate itself. (Direct hernia in this age group is so rare that it will not be considered.) Constipation, meatal stricture, coughing, crying, etc., are contributing causes responsible for the appearance of hernia only if the processus has not closed properly. Since the cause of hernia in children is an open sac, it seems logical to conclude that surgical treatment should consist of simple removal of that offending sac and nothing more.

One of the early steps in simplification of the surgical treatment of indirect inguinal hernia, especially in children, was taken by Ferguson[1] in 1899. He advised vehemently against elevating the structures of the cord from their normal position during surgical repair, but did advise plastic repair of the inguinal structures. He rose to oratorical heights when he said, "Tearing the cord out of its bed is without anatomic reason to recommend it, a physiologic act to suggest it, an etiologic factor in hernia, congenital or acquired, to indicate it, nor [does it give] brilliant surgical results to justify its continuance. Leave the cord alone, for it is the sacred highway along which travel vital elements indispensable to the perpetuity of our race."

The English and Scottish surgeons, notably Turner[2] in 1912 and MacLennon[3] in 1914, advised merely removal of the sac to the internal ring through a very small incision. Russel[4] in 1925 vigorously re-emphasized his long accepted doctrine of surgical removal of the sac only in the treatment of hernia in infants and children. Herzfeld[5] in 1938, in a report from the Royal Edinburgh Hospital for Sick Children, advised a small incision over

* Read before the American Surgical Association, Colorado Springs, Colorado, April 21, 1950.

the external ring, pulling down the sac, ligating it and closing the external ring with one stitch. The operation was performed in the outpatient department and the patient sent home following recovery from anesthesia. More recently Coles[6] has advised transection of the sac, transfixion and ligation of the proximal end as high as possible, and allowing the distal portion of the sac to drop back without further treatment.

Over against these sporadic pleas for simplicity in the treatment of hernia in children are innumerable articles advising prolonged truss treatment, delaying the operation until the child is two to four years old, and all sorts of complicated methods of plastic repair of the muscles and fascial structures. Too long there has been the false conception that infants and children are just small adults and should be treated as such in the solution of their surgical problems. The inguinal region is the lawful domain of the surgical resident. He has learned from his predecessors the Bassini technic and many of its modifications, and continues to use them indiscriminately on every hernia he can commandeer.

A book on hernia published in 1949 makes this general statement about hernia in children, "Complete removal of the sac, with obliteration of its neck and simple reconstruction of its parts, in a great majority of instances, ensures permanent cure." It is very difficult to get rid of the "reconstruction" idea in the surgical treatment of these hernias. It is freely granted that so long as repair of an inguinal hernia in an infant or child includes complete removal of the sac, recurrences will be rare regardless of what short of plastic repair is perpetrated upon the supporting structures of the inguinal region.

The sage advice of simply removing the hernial sac has been followed for 12 years without cause for regret. During the past four years approximately 600 hernias in infants and children have been operated upon at the Children's Memorial Hospital, employing largely the technic described below. For statistical purposes detailed case analyses and follow-up studies have been made on 100 infants below 18 months of age and of 100 children up to 13 years of age.

STATISTICS

In infants only 7 per cent of hernias were in females, while in children the percentage rose to 18 per cent. Three of the seven female infants had a sliding hernia of the ovary and tube. Hernia appeared with equal frequency on either side in children, but in infants 70 per cent occurred on the right side. In children 20 per cent were bilateral; in infants 17 per cent were bilateral. Hydrocele was associated with hernia in 9 per cent of infants and 16 per cent of children. At operation we have, with one exception, found a hernial sac associated with every hydrocele. We shall discuss this subject in greater detail later. Symptoms referable to the hernia, such as pain, irritability, colic and incarceration, relieved by operation, were present in 24 per cent of infants and 13 per cent of children.

Trusses had been or were being worn upon admission by 9 per cent of infants and 17 per cent of children. Many of the children had worn a truss for a number of years. Two children had developed a second hernia on the opposite side while wearing a truss. The hernia had not appeared for some time on the side where the truss was being worn. When the second hernia developed, operative correction was sought. Both sides were operated upon, and in each instance a narrow sac still open and about one and a half inches long was found on the side where the truss had been worn and the hernia "cured."

Parents fear incarceration of their baby's hernia and not without reason. Nineteen per cent of the infants entered the hospital with incarceration or

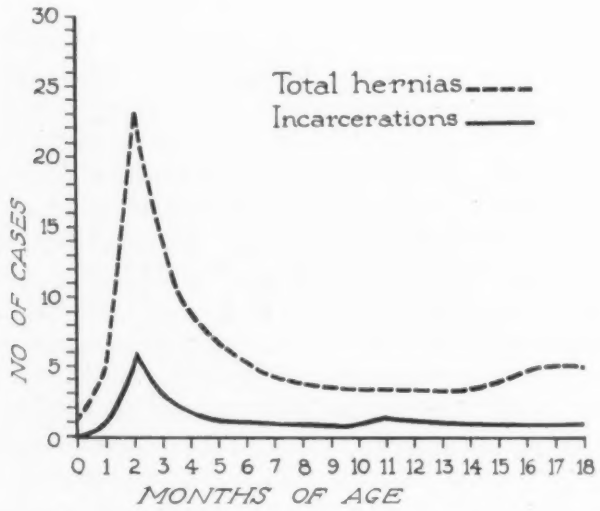

FIG. 1.—Incarceration is most common in early infancy.

with a history of recent incarceration reduced by a physician. Two infants developed incarceration while wearing a truss. Of 38 children below four months of age, 26 per cent were, or had been, incarcerated (Fig. 1). In children above 18 months of age only six per cent had incarceration.

The only death in this series of 600 cases occurred in a four-pound, six-weeks premature infant who was admitted to the hospital in extremis with a strangulated hernia. At operation the bowel was released and was questionably viable. Because the infant was near death, replacing the bowel in the abdomen seemed better judgment than resection. At autopsy the following day, rupture of the weakened bowel was found. Not only is incarceration dangerous because of possible bowel damage but also because of damage to the testicle. Six of the infants operated upon for incarcerated hernia had marked interference with the blood supply of the testicle; one had sloughed

out and had to be removed. In five cases the testicle, purplish black with congestion and questionably viable, was replaced in the scrotum. Three of these patients who were included in the follow-up study have, to our surprise, seemingly normal testicles. Incarceration is a real danger in hernia in infants.

OPERATION

If a definite diagnosis of inguinal hernia has been made in an infant or older child, operation is advised regardless of age provided the infant is otherwise normal and gaining weight. Such advice is often questioned by parents because of rumors they have heard that an infant cannot tolerate the operation, that the hernia will get well spontaneously, or that severe infections are apt to follow surgery. Pediatricians are becoming convinced that the

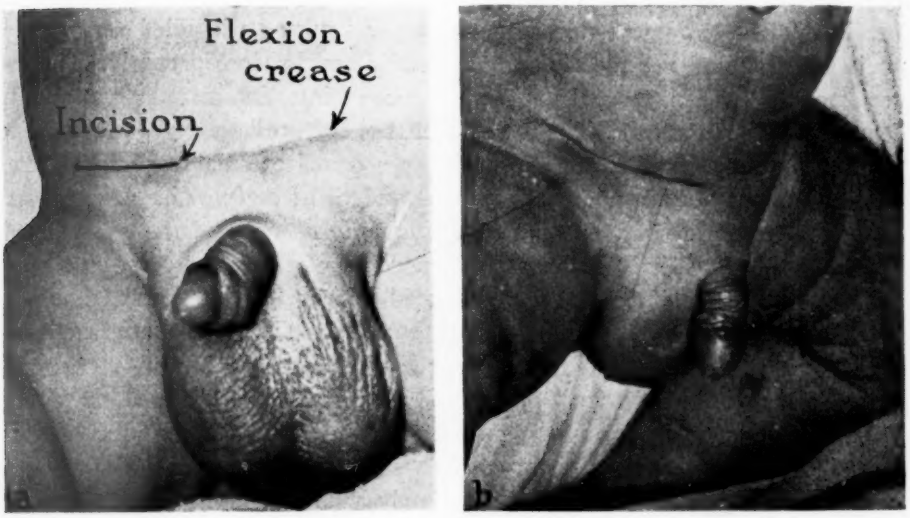

FIG. 2.—In all children below approximately two years of age a transverse incision is made in the suprapubic skin crease.

worrisome problem of an inguinal hernia in an infant can be solved safely, quickly and permanently by simple operation.

The child is carefully examined before being admitted to the hospital the afternoon before surgery. If there is the slightest sign of an upper respiratory infection or a history of exposure to contagion, the child is given a later appointment.

Ethyl chloride induction followed by open mask ether is the anesthesia of choice. The skin of the inguinal region, scrotum and penis are prepared for operation.

In all infants below approximately two years of age a one inch transverse skin incision is made in the crease which crosses the baby's abdomen in the

suprapubic region (Fig. 2). Such a skin incision is easier to close and less apt to become infected than an oblique incision, and because it follows the lines of cleavage it heals more smoothly with a scarcely visible scar and without annoying keloid formation. Cosmetic reasons for a minimal scar in the inguinal region carry little weight with the surgeon but are a source of pride to the mother. Why make an ugly scar anywhere when a neat one is possible with no more effort? In older children likewise, a transverse incision rather than one parallel with Poupart's ligament is made in the proper location.

The external oblique is opened parallel with its fibers, but in routine cases *the external ring is not opened* (Fig. 3). The lower half of the external oblique is retracted downward, while with a Halsted clamp the cremasteric fibers are split parallel with the cord, and the sac, easily recognizable by its gray-white color, is grasped and lifted up. With great gentleness the vessels and vas are dissected from the fragile sac as far upward as possible. The sac in infants is often as thin as gossamer and must be handled very gently or it will tear and become difficult to identify and to close properly. The interior of the sac is inspected for the presence of intestine or omentum and in female for ovary or tube. The sac is then twisted until the properitoneal fat appears or until the neck of the sac has been completely obliterated. The sac is then transfixed high with a silk suture and tied snugly. The excess is cut away. Attempts at transfixion and ligation of the neck of the sac without twisting will often lead to tearing and improper closure.

The external oblique fibers are coapted with a few interrupted fine silk sutures. The superficial fascia and subcutaneous fat are apposed and the skin is closed. In all infants the skin edges are apposed by buried interrupted, subcuticular stitches of 000000 silk. In older children the routine skin suture is used. A tiny strip of gauze not more than one-fourth of an inch wide is placed over the wound and sealed with a strip of water proof adhesive tape. The diaper is placed on infants immediately after surgery.

The patient is taken home the following day. No restrictions of any kind are placed on children up to approximately five years of age. The afternoon after operation the unrestrained children are walking about in their cribs. It is embarrassing to recall how 20 years ago these helpless children were strapped in bed for a week to ten days following repair of an inguinal hernia. Older children are cautioned against violent exercise for a week or two after operation depending upon age and personal characteristics.

The postoperative course is ordinarily smooth and free from complications. An occasional stitch abscess has developed, but there have been no gross infections. In routine uncomplicated cases hematomas of the scrotum have not occurred, due, we believe, without more than circumstantial evidence to support the claim, to the fact that the external ring has not been opened and that the cord has not been elevated. If the external ring is not opened, obviously it need not be closed and the danger of closing it too snugly and causing constriction of venous return is avoided.

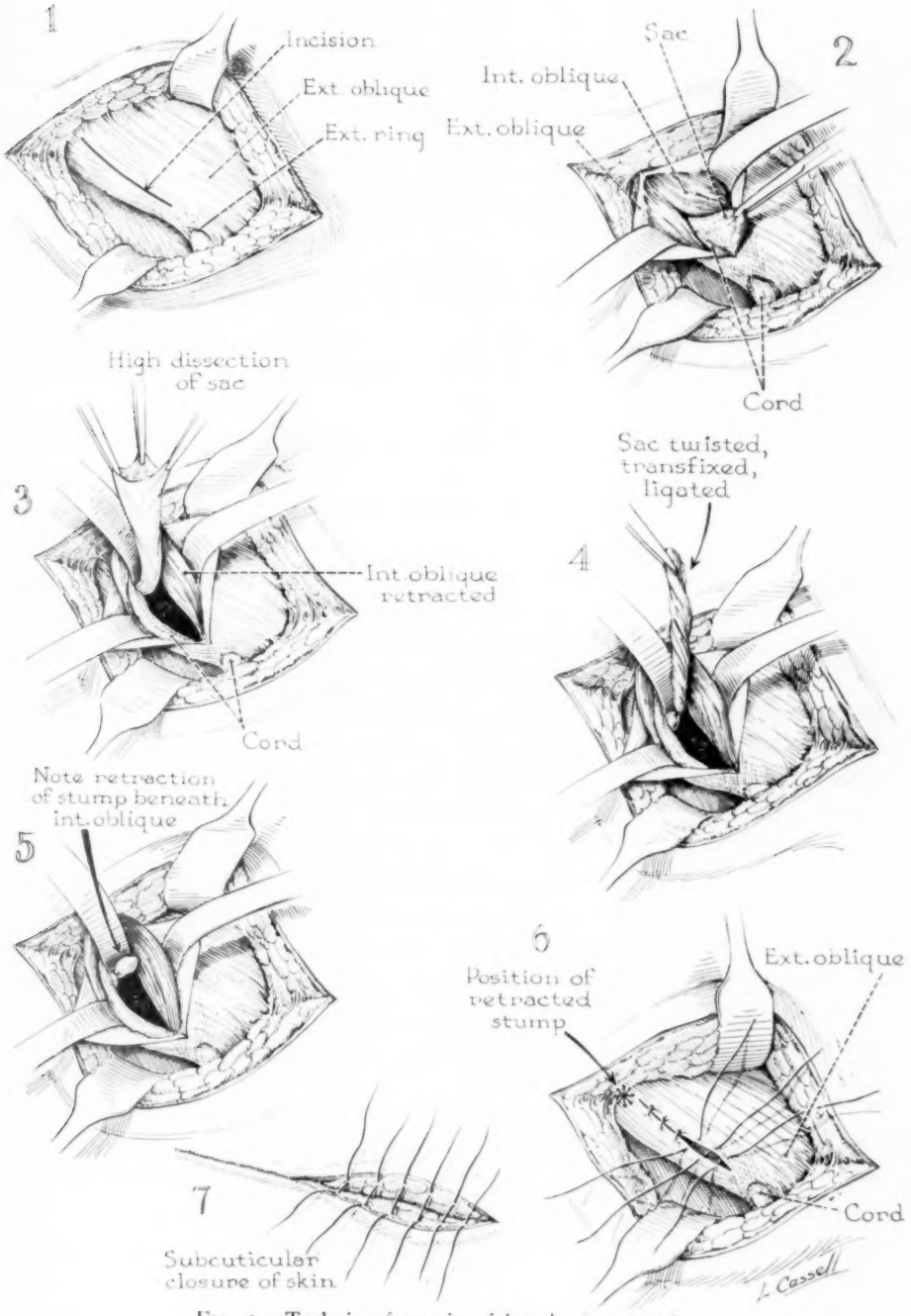

FIG. 3.—Technic of repair of hernia (see text).

RESULTS

A few days after the operation the anxious parents are grateful that the worrisome hernia has been repaired. Some had delayed operation because of natural fear of surgery; others had been fussing unsuccessfully with trusses for months or years; a few had done nothing but worry while they waited for their child to become "old enough for an operation."

No recurrence of a hernia has developed in 100 infants observed from six months to four years. Most of the patients had been operated upon at least two years before follow-up studies were made. In the older age group there was one questionable recurrence in a three-year-old child. At the second operation 11 months later, the intact sac was found with a silk suture in the side of it. Whether this was a true recurrence or a technical error on the part of the surgeon cannot be said, evidence suggests the latter.

No incidence of atrophy of the testicle has been observed following repair of an uncomplicated hernia. In 332 operations for infantile hernia Reinhard[7] reports consequent atrophy of the testicle in 12 patients (11 following the Bassini operation).

DISCUSSION

For thousands of years, trusses have been used for support of hernias and until the present age of safe anesthesia and intelligent surgery, offered the only means of relief. Only the weak and sickly child, unfit for surgery, should have the benefit of a truss as a temporary measure. Occasionally—but very occasionally—a proper truss will "cure" a small hernia in an infant below six months of age. Yarn trusses, popular for years, reassure the mother but do the infant no good. The least unsatisfactory truss for infants who must wear one is an elastic belt with a perineal strap which holds an inflated rubber pad over the inguinal region. For older children unfit for surgery, a spring truss is as good as any, but difficult to keep in place. The task of adjusting and keeping adjusted an effective truss on an infant, the difficulty of keeping the skin from becoming irritated, and the minimal chance of curing the hernia make the use of trusses in the young a poor substitute for quick and effective surgery.

Occasionally an infant will develop enormous hernias shortly after birth so large that many loops of bowel descend into the scrotum. Two such infants were seen, one, age one month, the other, age two months, both with bilateral hernias and openings in the inguinal region large enough to admit two fingers. In these two cases plastic repair was necessary to close the defect in the abdominal wall.

As stated above, hydroceles are commonly seen in children. Coles pointed out the association of hydroceles with hernias, in fact, went so far as to state that hydroceles can be cured by removing the hernial sac (Fig. 4). We can substantiate the almost invariable association of a hydrocele with a hernia—

often unsuspected. The easily available portion of the hydrocele sac is removed but the so-called "bottle operation" is never done in children. The hernial sac, often small and frequently with no demonstrable connection with the hydrocele, is routinely sought for and with but one exception has always been found and removed.

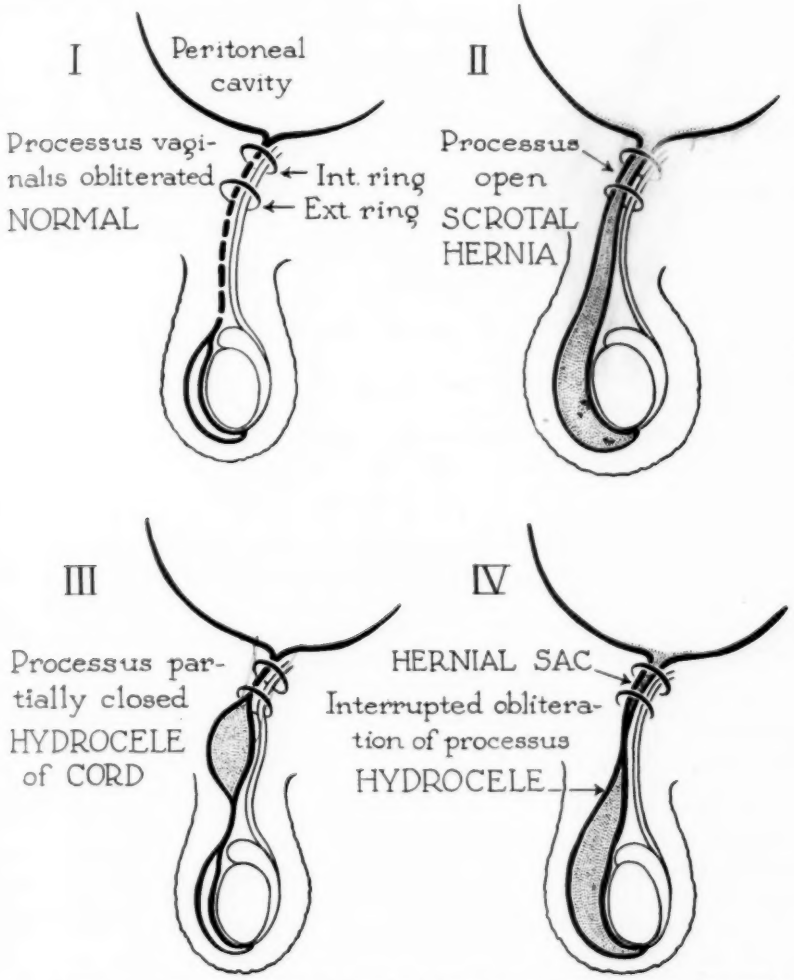

FIG. 4.—The pathology of inguinal hernia and hydrocele in the male child is very simple. There frequently is a tiny open connection between the hydrocele and the hernia.

Reasonable attempts should be made to reduce an incarcerated hernia in an infant rather than operate promptly, because of the difficulty in dissecting out and treating properly the edematous friable sac. While the baby industriously works on a pacifier re-enforced with sugar, the hernia can often be reduced by gentle pressure. If this maneuver fails, a sedative is given, adhesive strips are applied to the baby's legs, and enough traction is made by

weights hung over the end of the crib to lift all but the infant's head and shoulders from the mattress. Reduction usually occurs in an hour or two spontaneously or with the assistance of occasional slight pressure on the mass. Elective operation is performed later. Obviously, an irreducible hernia is promptly corrected surgically.

CONCLUSIONS

The treatment of the typical inguinal hernia in infants and children is surgical removal of the sac without elevating the structures of the cord and without any plastic repair of the muscles or fascia of the inguinal region.

Approximately 600 hernias in infants and children have been operated upon according to this method. Follow-up studies of 100 infants and 100 children revealed one questionable recurrence in a three-year-old child.

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Discussion.—Dr. Amos R. Koontz: I was very much interested in Dr. Potts' paper, especially with regard to his method of closure. I was always very much interested in Russell's work, ever since it first came out, but never had the temerity to use his method of simply ligating the sac and not making any other closure. I have asked a lot of other surgeons, too, but have not found anybody who had that much courage.

One of Russell's pupils recently published some figures on the use of his method in adults. He stated that he used Russell's method but also used a lot of other complicated reinforcing methods which were a little unorthodox, so it made me a little skeptical of the value of Russell's methods, in adults, at least.

It seems to me, though, that in addition to ligating and excising the sac, the little hole in the abdominal wall ought to be closed. There is a hole, of course, in the abdominal wall, through which the sac comes, and it could be closed very simply with one little suture. The hole is next to the opening through which the cord comes, and that hole might form the aperture for the appearance of a hernia later on. The structures there are the internal oblique and the transversalis fascia, and both can be grasped with a silk suture, and that opening around the cord can be made very snug without any difficulty whatsoever. That does seem to me to be a better procedure, although I must say that the statistics furnished here were certainly impressive.

As to the rest of the closure, I don't know of anybody who raises the cord in children. Some people do, I know, but I don't know anyone who does. It is almost impossible to tell, in children, whether the floor of the canal is solid or not. As a rule,

one can't get his finger into the opening of the sac at the internal ring and put it down on the inside to palpate from the inside to see whether the floor of the canal is solid or not because the structures are too small. However, it is so simple to put a few sutures between the conjoined tendon and the internal oblique *over the cord* that it seems to me that this is an added precaution that should be taken. After all we are dealing with a congenital defect, and who can tell how far the defect goes?

There is one thing that I have never been able to discover, and that is the shutter-like or valvelike action of the internal ring, which has been written about by Sir Arthur Keith and some of the other British observers. I have never been able to find those structures. Maybe it has been because of lack of keenness in observation on my part, but I have personally never been able to find them.

DR. DAMON B. PFEIFFER: I hadn't intended to discuss this paper, but it seems to me of sufficient importance to warrant a few words more, and to tell you of my own experience with this type of operation.

Some 20 years ago the Interurban Surgical Society joined in an expedition to the British Isles as guests of surgeons in London and Edinburgh, Glasgow and other places. It was a most enjoyable occasion. Vernon David and Jim Mason—who are here today, I think—were on that party.

Among other places, we stopped in Glasgow. Sir Archibald Young was at that time Professor of Surgery there, and among other places we were entertained at the Hospital for Sick Children, and there Mr. McClennan, whom Dr. Potts mentioned as one of the authors to whom he gave credit, demonstrated to us the operation of Sir William MacEwen, who was the predecessor of Sir Archibald Young.

Sir William MacEwen—who, as you all know, was a most ingenious man—really roamed the field of surgery in his day. He devised this operation for babies because they didn't have the babies' hospital at that time and they did it in the out-patient department, sending the baby home immediately.

It consisted of a small incision over the external ring, perhaps an inch long, through skin and superficial fascia which could be twitched up and down with small retractors. Then, without displacing the cord, the external spermatic fascia was teased apart with thumb forceps until the sac was reached. This was separated completely without opening, then twisted, transfixed at the base, and tied. The freed sac was then threaded on the needle, just as an angler puts a worm on a hook. The sac was then pushed down to the transfixed base, making a little ball. The short end of the suture was cut and the long end, still on the needle, was passed up under the arching fibers of the internal oblique and transversalis, which were pierced, and the internal ring thus pulled up beneath the arching fibers and there secured by a knot. The remaining long end of the suture was passed through the upper end of the slit in the aponeurosis and it was then closed by a running suture. The skin was closed, completing the operation.

I have standardized this operation ever since teaching it to my associates and assistants, and in all of our combined experiences, running into hundreds of cases now, there has been no mortality or morbidity or recurrence so far as I have been able to ascertain.

I do not think it is necessary to do anything to the internal ring at that age.

I congratulate Dr. Potts on rediscovering the value of this method and would like to lay a wreath on the tomb of Sir William MacEwen.

DR. LEO ELOESSER: These children, as Dr. Pfeiffer says, can be operated upon, ambulatory, and sent home, very well. I think if the mother takes the child home immediately, he will be less inclined to be upset and sick. In the second place, if you give the child one of those apparatuses that is known as a pacifier, or a nipple to suck, that is filled with a little absorbent cotton in sugar solution, and then use local anes-

thesia, it is quite feasible, and the baby isn't upset at all. He'll feed afterward just as he did before.

I quite agree with Dr. Potts that under circumstances not always as favorable as we have them here, the sooner we have the operation done, the better for the mother and the baby.

DR. WILLIS J. POTTS (in closing): I am especially grateful to Dr. Pfeiffer for his comments, and I would like to lay a few wreaths, too. I would like to lay some wreaths on the tombs of those who still do extensive plastic repair.

Dr. Lewis forgot to mention that the child goes home the day following the operation. Monday is "Hernia Day." The child comes in on Sunday afternoon, is operated on Monday morning, and goes home on Tuesday.

In answer to Dr. Koontz, I hope we can stimulate some bravery. Normally, the processus peritoneus closes. That is the way it should be; then there is no weakness in the internal ring. If we tie off the sac, there is no weakness, and that's all there is to it.

The comparison of a hernia in an infant with a hernia in an adult is something like the difference between fixing a Swiss watch and repairing a Big Ben alarm clock.

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